

A NEW ^{125}I -FIBRINOGEN TECHNIQUE FOR DETECTION
AND DEPTH LOCALIZATION OF POST-OPERATIVE
VENOUS THROMBOSIS

Studies in patients subjected to gynecologic surgery

Kurt Bernstein

Malmö 1981

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Kurt Bernstein

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From the Departments of Anaesthesia, Obstetrics and Gynaecology
and Radiation Physics, Malmö General Hospital, University of
Lund, Sweden.

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Abstract The reliability and sensitivity of the ^{125}I-fibrinogen uptake test (FUT) was improved by using an equipment that allowed frequent controls of its sensitivity. A new technique the ^{125}I-fibrinogen-sum-coincidence method (FSC), which can be used in combination with the conventional FUT for detecting deep venous thrombosis (DVT) was developed. With this new method the depths of the fibrin deposits detected by the FUT could be determined. Very good agreement was demonstrated between depth determinations of thrombi by the FSC-technique and by phlebography. The new technique permits differentiation between true DVT and superficial venous thrombosis. Altogether 354 patients subjected to gynecologic surgery were studied postoperatively with the improved FUT and 65 of them had signs of lower limb DVT with this test. 41 patients with a positive FUT were investigated with the FSC-technique as well, and in 37 of them the diagnosis of DVT was confirmed. Advanced age, and malignancy were preoperative risk factors for the development of DVT whereas the method of anaesthesia (general or epidural) had no significant influence on the rate of DVT. The five-fold increase in the rate of DVT after preoperative treatment with synthetic oestrogens necessitated a change in the preoperative administration of such drugs. The new FSC-technique offers the possibilities of both determining the true ^{125}I-activity in a thrombosis and of following its course for several weeks. It is recommended that thrombi with a maximum net-activity $>2\text{kBq}$ and with no sign of lysis when checked by the FSC-test should be treated.			
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REFERENCES

The present dissertation is based on the following papers, which will be referred to by the Roman numerals given below.

- I. Bernstein, K., Mattsson, S., Ulmsten, U. and Åstedt, B.
The ^{125}I -fibrinogen method for early diagnosis of venous thrombosis.
Vasc. Surg. 13, 33, 1979.
- II. Jacobsson, L., Mattsson, S., Bernstein, K., Ulmsten, U. and Åstedt, B. A method for determination of the depth of thrombi after injection of fibrinogen labelled with iodine-125.
Br. J. Radiol. 53, 668, 1980.
- III. Bernstein, K., Ulmsten, U., Åstedt, B., Jacobsson, L. and Mattsson, S. Incidence of thrombosis after gynecologic surgery evaluated by an improved ^{125}I -fibrinogen uptake test.
Angiology 31, 606, 1980.
- IV. Åstedt, B., Bernstein, K., Casslén, B. and Ulmsten, U.
Estrogens and postoperative thrombosis evaluated by the radioactive iodine method.
Surg. Gynecol. Obstet. 151, 372, 1980.
- V. Bernstein, K., Jacobsson, L., Mattsson, S. and Ulmsten, U.
Depth localization of thrombi and dynamic studies of post-operative thrombosis using the ^{125}I -fibrinogen-sum-coincidence method.
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1. INTRODUCTION

Deep venous thrombosis (DVT) is a serious disease because of the risk of pulmonary embolism (PE). Since the pioneering work of Virchow 1846, it has been known that pulmonary embolism generally originates from deep venous thrombosis in the legs or pelvis. Thromboembolism is a common cause of death. Thus, autopsy of all patients who died in Malmö General Hospital revealed thromboemboli in as many as one-third (Kaj, 1959 and Linell, 1965). In another study from the same hospital, 6 per cent of all deaths were shown to be caused by PE, only one-fourth of these cases having been diagnosed before death (Björnberg, 1962).

In a recent series of 508 carefully-performed randomized autopsies, 72 per cent of the patients had DVT and 69 per cent PE (Havig, 1977); Eighteen per cent of these 508 autopsies had lethal PE, and the connection between DVT and PE was also confirmed in this study. 75 per cent of cases with gross peripheral thrombosis had some form of PE. According to the same author, the most serious form of PE arose from DVT in the caval-ileo-femoral venous segments, but as many as 25 per cent of the lethal cases of PE arose from DVT solely in the veins of the calf. On the other hand, in about 80 per cent of the cases, femoral vein thrombosis was connected with calf-vein thrombosis, the latter being the most frequent type of DVT (80 per cent).

Venographic studies in patients have confirmed that proximal thrombosis is rarely seen alone but is nearly always combined with calf-vein DVT. This has led to the conclusion that DVTs originate in the veins of the calf and propagate centripetally (Nicolaidis et al., 1971). The results of scintigraphic studies support this conclusion (Kakkar et al., 1969). The connection between DVT and PE

has also been confirmed by objective methods such as the ^{125}I -fibrinogen uptake test (FUT) in conjunction with lung-scintigraphy (Browse et al., 1974) as well as by radionuclide venography (Smith et al., 1978).

The total incidence of PE in patients with DVT as verified by objective methods has been reported to be 18 per cent (Browse et al., 1974), 36 per cent (Lahnborg et al., 1974) and 50 per cent (Moreno Cabral et al., 1976). In the last study, about 50 per cent of the cases of pulmonary embolism were "silent" and thus only recognized on lung-scintigrams or pulmonary angiograms. However, while the most extensive ones arose from the ileo-femoro-popliteal venous segments, as many as one-third of them stemmed from calf or footveins.

The true incidence of DVT as detected by FUT in patients subjected to gynecologic surgery varies from 14 to 29 per cent (Walsh et al., 1974), (Kakkar et al., 1974), (Ballard et al., 1973) and is as high as 35 per cent in malignancy (Walsh et al., 1974). The clinical diagnosis of fatal pulmonary embolism has been made in 0.01 to 0.23 per cent of obstetric patients (Bauer, 1946), (De Bakey, 1954), (Gjöres, 1956). The total mortality in pulmonary embolism after gynecologic surgery has been found to vary between 0.01 and 0.87 per cent (Genton and Turpie, 1980).

2. METHODOLOGICAL ASPECTS

Clinical diagnosis of DVT.

The true incidence of DVT in humans is difficult to assess because of the unreliability of clinical signs and symptoms. Despite clinical diagnoses of DVT, 46 to 52 per cent of the patients had normal phlebographies (Haeger, 1965), (Nicolaidis et al., 1971). On the other hand, clinical signs are often minor or absent even in extensive thrombosis. With clinical examination alone, more than half of the DVT:s present were missed when controlled by radionuclide methods (Kakkar et al., 1976), (Flanc et al., 1968), (Lambie et al., 1971).

Clinical diagnosis of PE

The diagnoses of PE in patients by clinical signs only is notoriously difficult. Thus, clinical signs of DVT were found in only one-third of patients with PE (Sasahara et al., 1967), and none of the symptoms and clinical findings usually present, such as dyspnea, chest pain, coughing and tachycardia are pathognomonic for PE (Bell and de Mets, 1977).

Objective tests

Many objective tests to increase the accuracy in the diagnosis of DVT and PE have been introduced. All have their advantages and disadvantages and so far no ideal test for DVT, i.e., a test with high sensitivity and specificity, has been found. The diagnosis should be obtained rapidly, be safe and be able to be performed in a manner acceptable to the patient. It should be easy to perform and the results easy to interpret. To be used as a screening technique, it should also be non-invasive and inexpensive. Objective tests have shown a much higher incidence of DVT and PE than was believed earlier, when information was obtained only from clinical examination.

Objective tests for the diagnosis of PE

Available objective tests for the diagnosis of PE are only briefly mentioned here, because it was not the scope of this investigation to screen for PE. When negative, ventilation-perfusion scintigraphy excludes major PE. When positive to secure the diagnosis the results must be compared with those from a premonitory scintigraphy or to X-ray pictures of the lung taken both before and after the occurrence of PE. Pulmonary angiography is the generally accepted reference method but is unfortunately not free from side effects.

Objective tests for the diagnosis of DVT

There are several objective methods available to diagnose DVT:s

I. Radiological methods

1) Phlebography (X-ray contrast venography)

2) Radionuclide methods

a. Forming thrombi

Fibrinogen uptake test (^{123}I , ^{125}I , ^{131}I)

b. Preformed thrombi

Plasmin uptake test ($^{99}\text{Tc}^{\text{m}}$)

Streptokinase uptake test ($^{99}\text{Tc}^{\text{m}}$, ^{123}I , ^{125}I , ^{131}I)

Urokinase uptake test ($^{99}\text{Tc}^{\text{m}}$, ^{123}I , ^{125}I , ^{131}I)

Venography ($^{99}\text{Tc}^{\text{m}}\text{O}_4^-$, $^{99}\text{Tc}^{\text{m}}\text{-MAA}$, $^{99}\text{Tc}^{\text{m}}\text{-HAM}$, $^{99}\text{Tc}^{\text{m}}\text{-RBC}$)

II. Other methods

1) Pletysmography

a. Impedance pletysmography

b. Strain-gauge pletysmography

2) Ultrasound

3) Thermography

Phlebography

The technique used at Malmö General Hospital was introduced by Nylander. With the patient sitting and the lower leg hanging down, contrast medium is injected into a dorsal footvein. Frontal and lateral roentgenograms of the lower leg are obtained before and after the end of the injection. No tourniquet is used. The patient is afterwards placed supine and the leg is raised so as to accelerate the flow of contrast medium into the proximal veins and roentgenograms of these veins (Nylander, 1967) are then taken.

The phlebographic diagnosis of acute lower leg thrombosis is based on the following signs: 1) Non-visualisation of the deep crural veins, 2) a collateral flow through the superficial veins, and 3) patchy or streamline filling in the superficial veins. In cases where the phlebitic reaction is not severe enough to raise the subfascial pressure to a level above that of the venous pressure, the deep crural veins are visualized and the thrombi within them can easily be demonstrated as 4) filling defects (Brodelius et al., 1971).

The true accuracy of DVT detection by phlebographic technique is considered to be very high (Browse, 1978), and this is the method to which all other tests are compared. The sensitivity is highest when an experienced interpreter uses the technique to diagnose proximal thrombosis. On the other hand, the accuracy of the method decreases considerably when less experienced interpreters perform the investigations (Olsson, 1979). Furthermore, the deep femoral vein which constitutes the main venous outflow from the thigh can only be visualized in about 50 per cent of cases (Rabinov and Paulin, 1972), and the internal iliac vein is even less visualized by this technique. However, by injecting contrast medium directly into the common femoral vein or by pertrochanteric injection of intraosseous veins, the iliac veins can be opacified. Phlebography also causes a number of side-effects such as pain and discomfort in as many as 92 per cent of patients when conventional contrast medium is used (Olsson, 1979). Due to this fact and those presented below, phlebography should not be repeated. Thrombotic complications in phlebography has also been reported in 33 per cent of cases when high osmolarity contrast medium is used (Albrektson and Olsson, 1976). Subcutaneous extravasation of contrast medium in the foot has also been reported. There is a small but recognized risk in patients with coronary insufficiency and deaths from anaphylaxis after the intravenous injection of iodinated contrast medium has been reported (Shehadi, 1966). The phlebographic technique is most valuable in diagnosing proximal venous thrombosis, although the pelvic veins may be difficult to visualize by conventional techniques. However, since phlebography is not readily repeatable and because of its side-effects, it is not a suitable screening method for venous thrombosis after gynecologic surgery.

The ^{125}I -fibrinogen uptake test (FUT)

The fibrinogen uptake test came into clinical use in 1968 and has since been used extensively. The technique depends on the incorporation of circulating ^{125}I or ^{131}I labelled fibrinogen into a forming thrombus. The increased radioactivity can then be detected at the skin by an external detector. The observation by McFarlane,

1956 and 1963 that fibrinogen could be artificially labelled with radioactive iodine and still behave identically to endogenous fibrinogen was very important. Several investigators have since verified the clinical usefulness of FUT in expectant scanning, i.e., when labelled fibrinogen is injected into patients at risk to develop DVT before this happens. As to the usefulness of diagnostic scanning, i.e., when labelled fibrinogen is injected after the establishment of DVT, authors are not unanimous (Browse et al., 1971), (Mavor et al., 1972), (Olsson, 1979). Labelled fibrinogen (3.7 MBq) is given intravenously before the thrombus eventually forms, i.e., prior to an operation. The legs are then examined with a scintillation detector connected either to a ratemeter or a scaler immediately before operation and during 7-10 days postoperatively. The count-rate over any area measured on the lower limb is normally expressed in relation to the count-rate over the heart. If the "percentage uptake" (Negus et al., 1968) in any area increases by more than 10-20 per cent compared to adjacent areas, the corresponding contralateral area or to preoperative findings in the same area, this is suggestive of DVT (Becker, 1972), (Kakkar, 1972), (Negus et al., 1968). Venous thrombosis is then diagnosed if the scan remains abnormal at an examination 24 hours later.

The reported agreement between expectant scanning and venography is about 90 per cent in surgical patients. It is much less in orthopedic patients, because of the extravascular accumulation of labelled fibrinogen at the site of surgery which leads to scan abnormalities. The accuracy of the method normally diminishes at the proximal thigh because of the vicinity of the bladder and large blood vessels which results in an increased background count-rate. For the same reasons DVT in pelvic veins cannot be detected in a simple manner by FUT. False positive readings occur frequently due to superficial venous thrombosis, inflammatory reactions such as arthritis, local trauma with haematoma and marked oedema. Thus, these conditions should be excluded before using the test. The number of false negative results is very small and it is considered that the test is more accurate in the calf than venography and that small accumulations of radioactivity associated with negative venograms are thrombi which are too small to be detected by venography (Browse, 1978).

In diagnostic scanning, the agreement between FUT and venography varies between 70 and 80 per cent (Olsson, 1979), (Browse et al., 1971) one day after the injection of labelled fibrinogen. The number of false positive results is very high, 41 per cent of cases (Olsson, 1979).

The method is non-invasive, easy to perform and does not cause any pain. It can therefore be repeated whenever necessary. It does not need a skilled interpreter as is the case with phlebography. The three most significant advantages are:

1. Its sensitivity to small calf vein thrombosis which makes it suitable as a screening method.
2. The possibility of following the progress of a thrombus with or without therapy.
3. The possibility of assessing whether or not a thrombus is active.

Its two main disadvantages are 1) its relative insensitivity to thrombosis in the proximal thigh, although this has recently been refuted (Olsson, 1979), 2) the number of false positive results even in expectant scanning, e.g., about 20 per cent (Pollack et al., 1977) or 29 per cent of cases (Bernstein and Nylander, unpublished data). Also the large number of small subclinical thrombi detected by the method may create a problem for the clinician because the natural course of these thrombi is still unknown. The method cannot be used in orthopedic surgery because of postoperative accumulations of fibrin in the wound.

The patient is given daily 50-200 mg potassium iodide orally for 3 weeks to reduce the uptake in the thyroid of ^{125}I liberated when the ^{125}I -fibrinogen is metabolized. Like most radionuclide methods, it should not be used with pregnant women. Breast-feeding of infants has to be stopped for 3-4 weeks because of the high excretion of iodine in the mother's milk and the subsequent risk of thyroid damage in the child (Mattsson et al., to be published). There is a risk of hepatitis, but this is very slight.

It can be concluded that the method is generally accepted in

expectant scanning and is well suited as a screening method in non-orthopedic patients. Its use in diagnostic scanning is still under debate.

The $^{99}\text{Tc}^{\text{m}}$ -plasmin uptake test

In this test for established thrombi ^{125}I -fibrinogen is substituted for by $^{99}\text{Tc}^{\text{m}}$ -plasmin. The test is based on the fact that plasminogen-plasmin has a high affinity for thrombi because of lysin binding sites in the fibrinogen-fibrin molecule. This new radionuclide-method has been developed recently (Persson and Darte, 1977) and tried extensively in patients with suspected DVT (Olsson, 1979). Its sensitivity is equal to that of FUT, but the diagnosis is obtained much quicker. The specificity is not much better than that of FUT (Olsson, 1979). Streptokinase or urokinase labelled with ^{131}I or $^{99}\text{Tc}^{\text{m}}$ have been tried in the diagnosis of DVT (Darte et al., 1975), but experience with these tests is as yet limited.

Radionuclide venography

By injecting $^{99}\text{Tc}^{\text{m}}\text{O}_4^-$, $^{99}\text{Tc}^{\text{m}}$ labelled macroaggregates of albumin (MAA), $^{99}\text{Tc}^{\text{m}}$ labelled human albumin microspheres (HAM) or $^{99}\text{Tc}^{\text{m}}$ labelled red blood cells (RBC) into a foot vein and using a gamma-camera, images of both proximal leg veins and of lung perfusion can be obtained (Rosenthal and Grayson, 1979), (Webber et al., 1974), (Beswick et al., 1979). Thrombosis in deep proximal veins can be diagnosed either by dynamic criteria such as prolongation of mean transit time or derivation of blood flow into superficial veins (Nillius, 1978) or by using static criteria such as the adherence of macroaggregates to the thrombus (Webber et al., 1974).

Investigating asymptomatic patients after surgery of the hip Nillius (1978) found with the criteria he used a sensitivity of 80 per cent and a specificity of 98 per cent. A still higher sensitivity of 97 per cent using static criteria has been reported (Pollack, 1977). The sensitivity is higher in the pelvic veins (100 per cent) and in the femoral veins (96 per cent) than in the calf veins (69 per cent) (Kakkar, 1980). A lung scan can be obtained in the same examination as the venography.

Compared to contrast venography, pelvic veins are better visualized. Calf vein thrombosis is, however, poorly detected. Radionuclide venography is an invasive method, but simpler and not so painful to the patient as contrast venography. Moreover, there is less risk of anaphylaxis.

Plethysmography

Plethysmography is a non-invasive method of diagnosing DVT:s by measuring the change in the volume of the calf produced by venous congestion and the rate of emptying the calf after releasing the congestion. While several plethysmographic techniques have been used for the diagnosis of DVT, strain-gauge plethysmography and impedance plethysmography have been evaluated most extensively. Strain-gauge plethysmography was described by Hallböök and Göthlin (1971), (Hallböök and Göthlin, 1971). Low values of venous congestive volume (<1.8 ml/100 ml tissue) or venous emptying rate (<40 ml/minute x 100 ml tissue) were considered to indicate thrombosis.

Impedance plethysmography introduced by Wheeler et al., (1971), (Wheeler et al., 1972) is based on the observation that changes in the blood volume in the calf result in changes of the electrical impedance. Although the techniques mentioned above detect proximal thrombosis with high precision, they are very inaccurate in detecting calf vein thrombosis (Hallböök and Göthlin, 1971), (Wheeler et al., 1972), (Olsson, 1979). As a rule, the specificity is much higher than the sensitivity. In strain-gauge plethysmography, only 36% of the distal thrombi present were found (Olsson, 1979).

Plethysmography is very poor in detecting distal thrombi and the overall sensitivity is very low (63 per cent). Because no type of plethysmography can detect an early calf vein thrombosis, these tests are of no value as screening methods in the detection of early thrombi (Bergqvist et al., 1973). However, the method is non-invasive, cheap, easy to apply and may readily be repeated. It is not associated with any side-effects.

Ultrasound

The Doppler ultrasound technique of detecting venous thrombosis

was first used by Strandness et al., (1972) and by Sigel et al., (1972) (Strandness et al., 1972), (Sigel et al., 1972). A transducer which contains an ultrasound transmitter and a receiver is placed over a large vein. By utilizing the Doppler shift, changes in venous flow produced by respiration or by squeezing the calf can be observed as changes in the frequency of the ultrasound waves reflected. This implies that the veins between the squeezing hand and the transducer are patent. The interpretation of results is highly individual and dependent on the experience of the examiner. The method can only detect thrombi in larger veins, such as the femoral and popliteal veins and the obstruction caused by a thrombus must significantly occlude the vessel in order to be detected. As for plethysmography the specificity of the method seems to be higher than its sensitivity in experienced hands. Proximal venous thrombosis is correctly diagnosed in about 80 per cent of the cases but the method is insensitive to calf vein thrombosis. The main advantage of ultrasound is its simplicity. The apparatus is relatively cheap and the major veins can be checked quickly. A major disadvantage is that the technique cannot detect calf vein thrombosis, and even extensive thrombi in the large veins may be missed if the obstruction is only partial. Squeezing the calf muscle may dislodge thrombi and cause pulmonary embolism, but the risk is very small. In conclusion, the ultrasound technique seems suitable for the detection and follow-up of clinically suspected thrombi in the major veins. It is not suitable as a screening test for subclinical thrombosis in high risk patients.

Thermography

Thermography as a diagnostic method for detecting DVT was introduced by Cooke and Pilcher (1974) (Cooke and Pilcher, 1974). Using an infrared camera, the increased heat generated by a thrombus can be visualized. The warm areas are depicted in lighter colours than the cold areas which are displayed as black. The increased heat is caused by the inflammatory reaction itself and by the increased skin blood flow (derivated flow phenomenon, Nylander (1967)). Usually, when there is a major thrombosis in the calf or thigh the entire lower limb is seen to be warmer. The relative coolness normally observed over

the tibia and patella is reduced. All investigators agree that it is the total picture that gives the diagnosis and not the absolute temperatures or temperature-differences between the two legs. Localized "hot spots" of irregular appearance have been associated with DVT in the calf. In such cases, pictures of the posterior surface of the calf are valuable for the interpretation (Bergqvist and Hallböök, 1976).

In clinically-suspected thromboses, Cooke and Pilcher (1974) (Cooke and Pilcher, 1974) found 98 per cent agreement between thermography and phlebography. Bergqvist et al. found a diagnostic agreement of 90 per cent (Bergqvist et al., 1977). The same authors found a lower diagnostic agreement when thermography was used as a screening method for postoperative DVT and, comparing it with the ¹²⁵I-fibrinogen-uptake test (FUT), the diagnostic agreement was 81 per cent and the sensitivity 62 per cent but falling to 53 per cent in the calf. The specificity was 90 per cent (Bergqvist and Hallböök, 1978).

In a measurement series of our own which included 149 female patients >50 years old, consecutively operated on for uterine prolapse, thermography was compared with FUT in every patient on the seventh postoperative day. The total diagnostic agreement was 79 per cent. The sensitivity was 82 per cent and the specificity 78 per cent (Bernstein et al., 1979).

Of the 5 thrombi missed by thermography, 1 was superficial and 4 were small calf vein thrombi which lysed spontaneously.

Because of the high incidence of false positive results (22 per cent of cases), we investigated another series of patients with both preoperative and postoperative thermographies. Fifty-nine female patients more than 50 years of age who consecutively underwent hysterectomies were studied. The total agreement in this series between FUT and thermography was 86 per cent and higher than in the previous one mainly due to a higher specificity of thermography (90 per cent). The sensitivity dropped, however, to 63 per cent probably due to a low incidence of DVT and a high incidence of other preoperative abnormalities in the legs,

which made the interpretations difficult (Bernstein and Lindell, to be published).

In conclusion, there is only limited use for thermography as a post-operative screening method and then only if the following conditions are satisfied:

- 1) preoperative thermography is known and
- 2) the interpreter is very experienced.

The method should preferably be used to confirm thrombosis in patients with clinically-suspected DVT and especially when radio-nuclide methods are contraindicated, i.e., during pregnancy and while breast-feeding of infants.

After due consideration of the advantages and disadvantages of the objective methods available, it was concluded that FUT would be most suitable for screening thrombi after gynecologic surgery. However, already at the beginning of this work, it became evident that the existing methods had to be improved so as to become more reliable.

The aims of the present work have therefore been

A. Methodological considerations:

- a. To improve conventional FUT and
- b. To develop a new technique based on FUT for depth localization of DVT:s.

B. Clinical applications

- a. To establish with the improved and newly developed FUT technique the true incidence of DVT in high risk patients subjected to gynecologic surgery, and to define risk factors for the development of DVT such as the method of anaesthesia, duration of surgery, age and malignancy.
- b. To study any possible thrombo-genic effects of preoperatively-administered oestrogen
- c. To follow the course of postoperative DVT up to one month after surgery.

3. METHODOLOGICAL STUDIES; RESULTS AND DISCUSSION

a. Improvement of traditional FUT (I).

Initially we used a light portable detector with a one mm thick NaI(Tl) crystal 38 mm in diameter connected to a scaler for the detection of the increased ^{125}I -fibrinogen uptake. By using a scaler instead of a ratemeter it became possible 1) to increase the detectability, 2) to estimate the statistical uncertainty and 3) to carry out in a simple way daily controls of the sensitivity of the equipment. The performance of the detector was investigated in a water tank. A marked dependence with the variation in depth of the water of the ^{125}I -source was observed. At a depth of 1 cm, the sensitivity decreased to 50 per cent of that found when a ^{125}I -point source was applied to the water surface close to the detector. At a depth of 4 cm, the sensitivity dropped to 4 per cent. The rapid drop of sensitivity with increasing depth is mainly due to the fact that the volume from which the detector records the radioactivity varies more markedly with distance close to the detector than at a larger distance. This is characteristic not only for the type of detector studied but also for many other commercially available thrombosis detectors. From this, it is obvious that one of the most significant disadvantages of the present equipment is an exaggeration of superficially-located fibrin deposits in contrast to the rapidly-decreasing ability to detect deeply-located thrombi. One way to solve this problem would be to increase the distance between the detector and the skin. However, this would in turn demand for the same administered activity, an increased counting time unless decreased accuracy could be accepted.

In routine work, our equipment was found to be very reliable its sensitivity being constant from day to day. By raising the legs to an angle of 45° during recording, the number of false positive diagnoses caused by varicose veins could be minimized. The overall uncertainty of single measurements was small and the relative S.D. varied between $\pm 2.4\%$ for the heart and $\pm 5.4\%$ for the popliteal area (I, Table I). Daily measurements in 20 healthy patients during 7 consecutive days showed that the mean of the individual S.D.:s in day-to-day measurements of the count rate ratios between calf and heart was 2.0%, taking the count rate over the heart as 100%

(I, Table II). We thus chose to base the diagnosis of DVT on this small day-to-day variation in a non-thrombotic leg. Another reason for doing so was the high proportion of patients whose fibrinogen uptakes already differed preoperatively between the two legs due to anatomical causes such as varicose veins. Based on the data of table II, it was decided that an increase of 10% units in the "percentage count rate" over the same area of the calf between preoperative and postoperative recordings observed in measurements on two consecutive days indicated the presence of DVT. The improvements described led to a considerable increase in the reliability of the FUT.

- b. The development of a new technique for the depth localization of ^{125}I -fibrinogen uptake (II, III and V).

Already at the beginning of the present investigation it became evident that although reliable, the improved FUT gave too many false positive results as compared to phlebography. Such a high number of false positive findings (about 20 per cent of cases) had also been observed by other investigators (Gallus, 1975), (Pollack, 1977). The following conditions interfere with the detection of DVT using traditional FUT: superficial venous thrombosis, inflammatory joint diseases, inflammatory skin diseases and marked oedema of the leg. If the depths of the fibrin accumulations could be determined, it would be possible to differentiate between these mainly superficial uptakes and true DVT. A new method for determining the depth of the ^{125}I -fibrinogen deposits was therefore developed (II). It is based on the unique decay scheme of ^{125}I . This radionuclide decays first by electron capture (EC) and then by internal conversion (IC) or γ -emission (γ). On the average, 0.74 K X-rays are emitted per disintegration during EC while in IC 0.67 K X-rays are emitted as well as 7 per cent γ -radiation. In about half of the disintegrations K X-rays ($\bar{E} = 28 \text{ KeV}$) are emitted almost simultaneously both after EC and IC or γ and with a single NaI(Tl)-detector these coincident photons are registered as one peak with twice the main energy (56 keV). By taking the ratio between the coincident photons registered and the total number of photons recorded, one gets a parameter which is very sensitive to the distance between the de-

tector and the source of emission (II). 41 patients with fibrin accumulations detected by the improved FUT were studied with this new technique, the ^{125}I -fibrinogen-sum-coincidence method (FSC) (V). The depths of 24 suspected thrombi were measured both by phlebography and by the FSC-method. There was very close agreement between the depths recorded by the two methods. Sixteen thrombi whose depths could be measured very accurately at phlebography provide a good illustration of this. (V, Table I). The average depth to thrombi of the deep calf veins determined by the ^{125}I -fibrinogen-sum-coincidence method was 39 ± 8 mm from the medial side of the lower leg and 41 ± 10 mm from the posterior side. These mean values were significantly higher than those of the depth of ^{125}I -activities measured over legs free of thrombus (21 ± 3 mm as the mean from the medial side of the lower limb and 21 ± 4 mm as that from the posterior side of the lower limb) (V, Table II). Three cases of clinically-evident superficial venous thrombosis had their fibrin deposits located only 1, 7 and 9 mm beneath the skin surfaces. These findings gave rise to new criteria for detecting DVT: if the excess activity detected by conventional FUT is located deeper than 28 mm ($21 + 2$ S.D.) from either the medial or the posterior sides of the skin surface of the lower limb, this is suggestive of DVT. If, on the other hand, the excess activity is located less than 14 mm ($21 - 2$ S.D.) from the skin surface of either the medial or posterior side of the lower limb, superficial venous thrombosis is suggested. This technique makes it possible to enhance the reliability of conventional FUT by reducing the number of false positive results due to superficial venous thrombosis and other superficial fibrin accumulations.

4. CLINICAL APPLICATIONS

4.1 Material and methods

Table I. Indications for surgery in patients studied.

	Number of patients
I. Uterine prolapse (vaginal plasty)	216
II. Abdominal hysterectomies	138
1. Benign diseases	77
2. Malignant diseases	61
a) Without metastatic carcinoma	38
b) With metastatic carcinoma	23
Total	354

The distribution of the different tests used in patients with and without DVT is shown in table II.

The total number of DVT:s was 78 and the total number of cases of superficial thrombophlebitis was 11.

As can be seen from table II, both FUT and thermography were used as screening methods, the latter, however, only for 50 per cent of the patients. Phlebography and the ^{125}I -fibrinogen-sum-coincidence method were used to confirm the diagnosis when indications of DVT were found in traditional FUT. We have tried to facilitate the use of the ^{125}I -fibrinogen-sum-coincidence method by developing a mobile bedside equipment which will soon come into regular use.

Table II. Number of patients investigated by various methods.

Number of article	Diagnosis	FUT	Thermo- graphy	Phlebo- graphy	FSC
I	Patients with DVT	7	3	7	0
	Patients without DVT	29	0	0	0
II	Patients with DVT	9	5	9	9
	Patients without DVT	0	0	0	0
III	Patients with DVT	47	24	32	24
	Patients without DVT	229	125	0	0
IV	Patients with DVT	28	21	19	12
	Patients without DVT	148	116	1	0
V	Patients with DVT	65	30	45	37
	Patients without DVT	289	178	1	4
	Total patients with DVT	65	30	45	37
	Total patients without DVT	289	178	1	4

4.2 Results and discussion

a. Incidence of DVT and risk factors (III).

Of 276 consecutive patients more than 50 years old subjected to gynecologic surgery and investigated with the objective tests listed in table II, 51 patients had a total of 61 thrombi in their legs. (III)

Four patients had only superficial venous thrombosis while 47 patients (17 per cent of cases) had DVT. As can be seen in figure 1 (III), 10 per cent of the thrombi were located in the femoral and/or popliteal veins, 20 per cent in tibial or fibular veins, 60 per cent in calf muscle veins and 10 per cent in superficial veins. Eight patients had multiple thrombi.

As shown in figure 2 (III), the separation in depth between superficial venous thrombi (< 14 mm) and deep venous thrombi (> 28 mm) in 11 patients investigated with the ^{125}I -fibrinogen-sum-coincidence method was good. Phlebographic controls showed a close agreement between the two methods of determining the depths of thrombi.

The total incidence of DVT was 17 per cent. Table II (III) shows that patients undergoing hysterectomies for benign diseases had the lowest rate of DVT (11 per cent) whereas those with hysterectomies for malignant diseases had the highest (36 per cent). Patients operated on for uterine prolapse had an intermediate DVT frequency (15 per cent). There was no difference between the incidence of DVT in patients with epidurals and those who had general anesthesia. The duration of surgery was not a significant factor in this study. The rather low incidence of DVT in patients operated for uterine prolapse in spite of advanced age did not indicate any untoward effect of the leg-bearers used in these patients. Advanced age, malignancy and pre-operative oestrogen treatment were the three dominating risk factors for the development of DVT. For patients receiving prophylaxis with dextran 70 (46 patients) or dihydroergotamin (DHE) (40 patients), the incidence of DVT was 20 per cent and 23 per cent respectively. These figures do not indicate any effect of the prophylaxis given and, for ethical reasons and against the background of earlier studies, we did not carry out control studies with placebo. However, for dextran 70, it is known that the rate of DVT as detected by FUT may be quite high, although these "dextran thrombi" lyse more readily and are therefore not liable to cause any dangerous PE. The low incidence of PE clinically detected during the time in the ward (≈ 1 per cent) with no mortality did not change after we reviewed the patients' records several months after surgery.

We conclude that the low incidence of PE in patients with asymp-

matic DVT detected by postoperative screening observed in this study may be ascribed to the combined effects of prophylaxis with dextran 70 or dihydroergotamin and early treatment with full dose heparin. Our incidence of PE is fully comparable with that of a group of high risk patients receiving postoperative anticoagulant prophylaxis (Skinner and Salzman, 1967).

b. Influence of oestrogens (IV)

In female patients more than 50 years of age operated on for uterine prolapse, the postoperative rate of DVT increased five-fold (to 50 per cent) following preoperative administration of synthetic oestrogens. Ethinyl-oestradiol was administered either as 50 µg daily for three weeks before surgery or as 200 µg daily for 12 days before operation. The resulting frequency of DVT was the same in the two groups. It thus seems as if the duration of preoperative administration of oestrogen is as important as the dosage. It is suggested that surgery and administration of ethinyl-oestradiol might have synergistically depressed the fibrinolytic defence system against thrombosis. It is known that ethinyl-oestradiol depresses the activator activity in the vessel walls (Åstedt, 1971). Hence, oestrogens should not be given preoperatively to such patients and, if administered as oral contraceptives or to mitigate climacteric inconvenience, they should be discontinued before surgery.

c. Course of postoperative DVT (V).

By using the ^{125}I -fibrinogen-sum-coincidence technique, the course of thrombi could be followed for up to one month after surgery. The thrombi could be characterized according to their elimination rates and to their maximum net-activities on the 7th postoperative day. High maximum net-activities $>2 \text{ kBq}$ (0.5% of the injected activity) and low elimination rates were associated with major DVT:s and PE:s. Low maximum net activities $<800 \text{ Bq}$ (0.2% of the injected activity) were associated with total lysis of the thrombi within one month. There was a highly significant correlation between the maximum net-activities of postoperative thrombi and their respective ratios of

$$\frac{T_{1/2} \text{ thrombosis}}{T_{1/2} \text{ blood}} \quad (\text{figure 2, V}).$$

The relation between these two parameters could be described by a power function (for discussion see V). Many attempts to classify thrombi according to the amount of radioactivity they contain which can be detected at the limb-surface have already been made. In one of these studies (Wolf and Hume, 1974), a positive correlation was found between the phlebographic size of thrombi and the total excess radioactivity detected over the calf. In this study, however, no correction was made for the depth of the radioactivity nor was the further course of the thrombi studied by these authors. From the results of our study, it seems to be possible to predict the severity and future course of a postoperative DVT by determining its maximum net-activity and half-life ratio.

5. GENERAL SUMMARY AND CONCLUSIONS

For the detection of DVT by FUT, it is important to use equipment which offers the possibility of continuous monitoring of its sensitivity. In the present study, we have found a light portable detector with a very thin NaI(Tl) crystal connected to a scaler to be reliable. By using this detector, we obtained a very small standard deviation in day-to-day measurements in normal legs. It thus became possible to make the diagnosis of DVT more accurate. Using the improved technique, the increase in the "percentage count rate" necessary to indicate a DVT could be reduced from 20 to 10 per cent. The only disadvantage with the detector used was an exaggeration of superficially-located fibrin deposits and consequently an underestimation of deeply-located thrombi.

For this reason, the ^{125}I -fibrinogen-sum-coincidence method (FSC) was developed. The new technique enables determination of the depths of thrombi and an exact differentiation between superficial thrombophlebitis and true DVT. The new FSC-test thus eliminates one of the main disadvantages which has hitherto limited the use of the original FUT. In fact, the accuracy of the combined methods (FUT/FSC) might even be superior to phlebography in diagnosing small calf vein thrombi.

It is concluded that some important factors increase the risk of developing DVT in patients subjected to gynaecologic surgery, namely

advanced age, malignant disease, and preoperative oestrogen treatment. On the other hand, neither the method of anesthesia (general or epidural) nor the the duration of operation had any significant influence on the incidence of DVT. The use of leg bearers in patients operated upon for uterine prolapse was not accompanied by any increased frequency of DVT.

The five-fold increase in the rate of DVT observed after preoperative treatment with synthetic oestrogens argues for a recommendation to avoid the preoperative administration of such drugs.

With the new technique, it might be possible to identify patients at risk to develop manifest PE, since in our three cases of serious PE, all had positive leg scans with very characteristic radioactive features (high maximum net activity and a slow elimination rate of this activity). However, a much greater number of patients have to be screened for PE before any definite conclusions can be drawn. The elimination rate of a thrombus can be followed postoperatively for up to one month and this permits a continuous evaluation of the course of a thrombus. Thus, the need for phlebography will presumably be reduced in the future.

The following measures are proposed so as to prevent DVT and PE:

1. Women on oestrogen treatment should have this discontinued for one month before elective surgery.
2. All patients more than 40 years of age in whom laparotomy is performed should receive prophylactic treatment and should be monitored for the development of DVT by FUT.
3. Patients operated upon for malignancy as well as patients with a previous history of DVT should, irrespective of age, also receive prophylaxis and be screened by the FUT.
4. When the FUT results are suggestive of DVT, the ^{125}I -fibrinogen-sum-coincidence method (FSC) should be performed to confirm the diagnosis and assess the risk of PE.

As routine prophylaxis, either dextran 70 or low-dose-heparin according to Kakkar could be used, but neither of these drugs is

100 per cent effective. Patients who, in spite of this prophylaxis, show evidence of DVT by FUT/FSC should be treated by full dose heparin. Which of the small subclinical DVT:s detected by the original FUT should be treated, is still under discussion. It is our opinion that calf-vein thrombi checked by FSC and with a maximum net-activity of more than 2 kBq should be treated because in our study pulmonary emboli were associated with such thrombi. If such DVT:s are not treated, they must be very thoroughly followed by the FSC-method during the first month after surgery. It is concluded that the results and suggestions outlined here will consistently minimize the risk for the development of PE.

REFERENCES

- ALBRECHTSSON, U. & OLSSON, C.G.: Thrombotic side-effects of lower limb phlebography.
Lancet 1, 723, 1976.
- BALLARD, K.M., BRADLEY-WATSON, P.J., JOHNSTONE, F.D., KENNEY, A. & MCCARTHY, T.G., CAMPBELL, S. & WESTON, J.: Low doses of subcutaneous heparin in the prevention of deep vein thrombosis after gynaecological surgery.
J. Obstet. Gynaecol. Br. Cwlth. 80, 469, 1973.
- BAUER, G.: Thrombosis; early diagnosis and abortive treatment with heparin.
Lancet 1, 447, 1946.
- BECKER, J.: The diagnosis of venous thrombosis in the legs using J-labelled fibrinogen.
Acta Chir. Scand. 138, 667, 1972.
- BELL, W.R. & deMETS, D.L.: The clinical features of submassive and massive pulmonary emboli.
Am. J. Med. 62, 355, 1977.
- BERGQVIST, D., EFSING, H.O. & HALLBÖÖK, T.: Termografi - en icke-invasiv metod för trombosdiagnostik - en jämförelse med flebografi.
Läkartidningen 73, 4429, 1976
- BERGQVIST, D., EFSING, H.O. & HALLBÖÖK, T.: Thermography - A non-invasive method for diagnosis of deep venous thrombosis.
Arch. Surg. 112, 600, 1977
- BERGQVIST, D. & HALLBÖÖK, T.: Thermography in screening postoperative deep vein thrombosis: A comparison with the ^{125}I -fibrinogen test.
Br. J. Surg. 65, 443, 1978.

BERGQVIST, E., BERGQVIST, D., BRONGE, A., DAHLGREN, S. & HALLBÖÖK, T.:
Diagnosis of venous thrombosis in the lower limbs: a comparative
study between ^{125}I -fibrinogen test, strain gauge plethysmography
and phlebography.

Ups. J. Med. Sci. 78, 191, 1973.

BERNSTEIN, K. & NYLANDER, G.: Unpublished data.

BERNSTEIN, K., LINDELL, S.-E., MATTSSON, S., ULMSTEN, U. & ÅSTEDT, B.:
Comparison between thermography and ^{125}I -fibrinogen test for
screening of post-operative thrombosis after gynaecologic surgery.
Acta thermographica 4 (3), 108, 1979.

BERNSTEIN, K., LINDELL, S.-E.: To be published.

BESWICK, W., CHMIEL, R., BOOTH, R., VELLAR, I., GILFORD, E. &
CHESTERMAN, C.N.: Detection of deep venous thrombosis by
scanning of $^{99\text{m}}$ technetium-labelled red-cell venous pool.
Brit. Med. J. 1, 82, 1979.

BJÖRNBERG, Ö.: Dödande lungemboli hos gamla patienter med intern-
medicinska sjukdomar.
Nord. Med. 68, 1548, 1962.

BRODELIUS, Å., LÖRINC, P. & NYLANDER, G.: Phlebographic techniques
in the diagnosis of acute deep venous thrombosis of the lower limb.
Amer. J. Roentgenol. 111, 794, 1971.

BROWSE, N.: Diagnosis of deep vein thrombosis.
Brit. Med. Bull. 34, 163, 1978,

BROWSE, N.L., CLEMENSON, G. & CROFT, D.N.: Fibrinogen - detectable
thrombosis in the legs and pulmonary embolism.
Brit. Med. J. 30, 603, 1974.

BROWSE, N.L., CLAPHAM, W.F., CROFT, D.N., JONES, D.J., LEA THOMAS, M.
& OLWEN WILLIAMS, J.: Diagnosis of established deep vein thrombosis
with the ^{125}I -fibrinogen test.

Br. Med. J. 4, 325, 1971.

COOKE, E.D., & PILCHER, M.F.: Deep vein thrombosis: preclinical
diagnosis by thermography.

Br. J. Surg. 61, 971, 1974.

DARTE, L., OLSSON, C.G. & PERSSON, R.B.R.: $^{99}\text{Tc}^{\text{m}}$ -labelling of strepto-
kinase and its use for detection of deep vein thrombosis using
scintillation camera and hand detector.

Proc. XIII Int. Meeting Soc. Nucl. Med., Copenhagen 1975, in
Nuklear-medicin 1977, Schattauer Verlag, Stuttgart-New York.

DeBAKEY, M.: Collective review: Critical evaluation of the problem of
thromboembolism.

Surg. Gynecol. Obstet. 98, 1, 1954.

FLANC, C., KAKKAR, V.V., & CLARKE, M.B.: The detection of venous
thrombosis of the legs using ^{125}I -labelled fibrinogen.

Brit. J. Surg. 55, 742, 1968.

GALLUS, A.S.: ^{125}I -fibrinogen leg scanning. In prophylactic therapy of
deep vein thrombosis and pulmonary embolism, ed Fratanoni, J. &
Wessler, S., p.77, Bethesda NIH, 1975.

GENTON, E., & TURPIE, A.G.G.: Venous thromboembolism associated with
gynecologic surgery.

Clin. Obstet. and Gynec. 23, 209, 1980.

GJÖRES, J.E.: The incidence of venous thrombosis and its sequelae
in certain districts of Sweden.

Acta chir. scand. suppl. 206, 1, 1956.

HAEGER, K.: Den kliniska trombosdiagnosens (O) tillförlitlighet.

Läkartidningen 62, 1067, 1965.

HALLBÖÖK, T., & GÖTHLIN, J.: Strain gauge plethysmography and phlebography in diagnosis of deep vein thrombosis.

Acta Chir. Scand. 137, 37, 1971.

HAVIG, Ö.: Deep vein thrombosis and pulmonary embolism. An autopsy study with multiple regression analysis of possible risk factors.

Acta Chir. Scand. Suppl. 478, 42, 1977.

KAIJ, K.: Tromboembolifrekvensen i ett obduktionsmaterial.

Läkartidningen 56, 1437, 1959.

KAKKAR, V.V., HOWE, C.T., FLANC, C. & CLARKE, M.B.: Natural history of postoperative deep-vein thrombosis.

Lancet 2, 230, 1969.

KAKKAR, V.V. et al.: Heparin versus dextran in the prevention of deep-vein thrombosis.

Lancet 2, 118, 1974.

KAKKAR, V.V.: The diagnosis of deep vein thrombosis using ^{125}I -fibrinogen test.

Arch. Surg. 104, 152, 1972.

KAKKAR, V.V.: Diagnosis of deep vein thrombosis. In the British Council Course 034 on thromboembolic disease, 1980.

LAHNBORG, G., BERGSTRÖM, K., FRIMAN, L. & LAGERGREN, H.: Effect of low dose heparin on incidence of postoperative pulmonary embolism detected by photoscanning.

Lancet 1, 329, 1974.

LAMBIE, J.M., MAHAFFY, R.G., BARBER, D.C., KARMODY, A.M., SCOTT, M.M. & MATHESON, N.A.: Diagnostic accuracy in venous thrombosis.

Brit. Med. J. 2, 142, 1970.

LINELL, F.: Heparinsymposium. Jönköping, 1965.

MATTSSON, S., BERNSTEIN, K. & LÖFGREN, O.: Case report to be published.

- MAVOR, G.E., MAHAFFY, R.G., WALKER, M.G., DUTHIE, J.S., DHALL, D.P.,
GADDIE, J. & REID, G.F.: Peripheral venous scanning with ^{125}I -
tagged fibrinogen.
Lancet 1, 661, 1972.
- McFARLANE, A.S.: Labelling of plasma proteins with radioactive iodine.
Biochem. J. 62, 135, 1956.
- McFARLANE, A.S.: In vivo behaviour of I^{131} -fibrinogen.
J. Clin. Invest. 42, 346, 1963.
- MORENO-CABRAL, R., KISTNER, R.L. & NORDYKE, R.A.: Importance of calf
vein thrombophlebitis.
Surgery 80, 735, 1976.
- NEGUS, D., PINTO, D.J., LeQUESNE, L.P., BROWN, N. & CHAPMAN, M.:
 ^{125}I -labelled fibrinogen in the diagnosis of deep-vein thrombosis
and its correlation with phlebography.
Br. J. Surg. 55, 835, 1968.
- NICOLAIDES, A.N., KAKKAR, V.V., FIELD, E.S. & RENNEY, T.G.: The
origin of deep vein thrombosis: a venographic study.
Brit. J. Radiol. 44, 653, 1971.
- NILLIUS, S.A.: On thromboembolism after total hip replacement.
Dissertation, Malmoe General Hospital, University of Lund,
Malmoe, Sweden, 1978.
- NYLANDER, G.: Phlebographic diagnosis of acute deep leg thrombosis.
Acta Chir. Scand. suppl 387, 30, 1967.
- OLSSON, C.G.: On the diagnosis of deep vein thrombosis.
Dissertation, Dept. of Clinical Physiology, University of Lund,
Sweden, 1979.
- PERSSON, B.R.R. & DARTE, L.: Labelling plasmin with technetium-99m
for scintigraphic localization of thrombi.
J. Appl. Rad. Isotop. 28, 97, 1977.

- POLLACK, E.W., WEBER, M.M. & VICTORY, W.: Fibrinogen uptake test.
Criteria for interpretation of results in patients with venous thrombosis.
Amer. Surgeon 43, 119, 1977.
- POLLACK, E.W.: The choice of test for diagnosis of venous thrombosis.
Vasc. Surg. 11(4), 219, 1977.
- RABINOW, K & PAULIN, S.: Roentgen diagnosis of venous thrombosis in the leg.
Arch. Surg. 104, 134, 1972.
- ROSENTHALL, L. & GREYSON, N.D.: Observations on the use of ^{99m}Tc albumin macroaggregates for the detection of thrombophlebitis.
Radiology 94, 413, 1970.
- SASAHARA, A.A., CANNILLA, J.E., MORSE, R.L., SIDD, J.J. & TREMBLAY, G.M.:
Clinical and physiological studies in pulmonary thromboembolism.
Am. J. Cardiol. 20, 10, 1967.
- SCHMIDT, K.G., RASMUSSEN, J.W. & FRIGÅRD, E.: Scintigraphic investigation of the legs and lungs in suspected cases of deep vein thrombosis and pulmonary embolism.
Dan. Med. Bull. 25, 159, 1978.
- SHEHADI, W.H.: Clinical problems and toxicity of contrast agents.
Am. J. Roentgenol. 97, 762, 1966.
- SIGEL, B., FELIX, W.R., POPKY, G.L. & IPSEN, J.: Diagnosis of lower limb venous thrombosis by Doppler ultrasound technique.
Arch. Surg. 104, 174, 1972.
- SKINNER, D.B. & SALZMAN, E.W.: Anticoagulant prophylaxis in surgical patients.
Surg. Gynecol. Obstet. 125, 741, 1967.
- STRANDNESS, D.E. & SUMMER, D.S.: Ultrasonic velocity detector in the diagnosis of thrombophlebitis.
Arch. Surg. 104, 180, 1972.

VIRCHOW, R.: Über die Verstopfung der Lungenarterie.

FRORIEPS N: Notizen Nr 794, 1846. In Klassiker der Medizin:
Thrombose und Embolie. Verlag von J.A. Barth, Leipzig, 1910.

WALSH, J.J., BONNAR, J. & WRIGHT, F.W.: A study of pulmonary embolism
and deep leg vein thrombosis after major gynaecological surgery
using labelled fibrinogen-phlebography and lungscanning.
J. Obstet. Gynaecol. Br. Cwlth. 81, 311, 1974.

WEBBER, M.M., POLLACK, E.W., VICTERY, W. et al.: Thrombosis detection
by radionuclide particle (MAA) entrapment. Correlation with
fibrinogen uptake and venography.
Radiology 11, 645, 1974.

WHEELER, H.B., PEARSON, D., O'CONNELL, D. & MULLICK, S.C.: Impedance
plethysmography: technique, interpretation and results.
Arch. Surg. 104, 164, 1972.

WHEELER, H.B., O'DONELL, J.A. & ANDERSSON, F.A.: Bedside screening
for venous thrombosis using occlusive impedance plethysmography.
Angiology 26, 199, 1975.

WOLF, E. & HUME, M.: The semi-quantitative classification of thrombus
size by the ¹²⁵I-labelled fibrinogen technique.
Thromb. Res. 4, 757, 1974.

ÅSTEDT, B.: Low fibrinolytic activity of veins during treatment with
ethinyloestradiol.
Acta. Obstet. Gynecol. Scand. 50, 279, 1971.

The ^{125}I -Fibrinogen Method for Early Diagnosis of Venous Thrombosis

Kurt Bernstein, M.B.B.S., F.I.C.A., Sören Mattsson, Ph.D.,
Ulf Ulmsten, M.D., and Birger Åstedt, M.D.

MALMO, SWEDEN

Abstract

In vitro and in vivo experiments were performed with a scintillation detector designed for ^{125}I -fibrinogen measurements. The sensitivity of the detector was tested in a water phantom. The relative count rate of 100 when the ^{125}I point source was applied to the water surface decreased to 50 at a water depth of 1 cm to 14 at 2.5 cm, and to 4 at 4 cm. Measurements on normal patients showed that the individual standard deviation of day-to-day measurements of the count rate on the calf was $\pm 2.0\%$ of the count rate over the heart. Based on these data, we decided that a 10% increase in this "percentage count rate" between preoperative recordings and recordings made at 2 consecutive days was suggestive of thrombosis. Of 36 high-risk patients subjected to surgery, 7 (20%) filled this criterion.

Introduction

Clinical judgment is an uncertain method for diagnosing deep venous thrombosis (DVT). It has been claimed that only 50% of all cases of DVT are detected at clinical examination,^{1,3} and Haeger⁴ found that the phlebographies were normal in 46% of a series of patients with clinically diagnosed DVT.

That the diagnosis of DVT is an important clinical problem is obvious from the fact that of all the patients who died at our hospital, autopsy revealed thromboemboli in as many as one-third.^{5,6} Later, the corresponding frequency of pulmonary emboli for the department of internal diseases at autopsy was found to vary between 15 and 20%. In another study, 6% of all deaths proved to have been caused by pulmonary emboli, and only one-fourth of these cases had been suspected before the patient died.⁷ Such figures are far from satisfactory.

Ambrus and associates⁸ were the first to use isotopes to detect venous

From the Departments of Anaesthesia, Obstetrics and Gynaecology, and Radiation Physics, University Hospital of Malmö, Sweden.

thrombi. In 1960, Hobbs and Davies⁹ evaluated the method in rats. They used ^{131}I -labeled fibrinogen. Palco and colleagues¹⁰ used the method on humans in vivo. In 1965 Atkins and Hawkins¹¹ introduced ^{125}I as a tracer instead of ^{131}I . The ^{125}I -fibrinogen method proved useful in detecting small early thrombosis of the lower limbs, where it could be used as a screening method.⁹ The many small or "subclinical" thrombi that can be diagnosed with the ^{125}I -fibrinogen method are of less clinical significance because most of them produce no symptoms and are dissolved spontaneously by the fibrinolytic defence system. Only those lower limb thrombi that extend to the popliteal and femoral veins should be treated.² These "subclinical" thrombi are, however, of great interest since they can be utilized in the study of the origin of postoperative thrombosis and the effect of thrombotic prophylaxis.

When the ^{125}I -fibrinogen method is used the measuring technique is of great importance, especially for detecting small early fibrin deposits. The aim of the present study was to evaluate, in vitro and in vivo, a light ^{125}I detector to be used in clinical studies of early thrombosis in women subjected to high-risk gynecologic operations.

Materials and Methods

Measuring Technique

The photon radiation of low energy emitted when ^{125}I decays is dominated by characteristic x-rays from tellurium. The weighted mean value of the photon energies of interest is 28.3 keV. To register these photons we used a 1 mm NaI (Tl) crystal 38 mm in diameter (Eberline, MS-2F, Eberline Instrument Corp., Santa Fe, NM). The detector has a 0.025 mm aluminum window, and from the side it is shielded by 2.8 mm Al. No extra collimation of the detector was used. The energy window of the single-channel analyzer was set at 28 ± 7 keV. The sensitivity of the equipment was checked daily by means of the same ^{125}I point source placed at a fixed position to the detector.

Experimental Procedure in Vitro

Evaluation of the clinical measurements requires knowledge of the ability of the equipment to detect ^{125}I in soft tissue at various distances from the detector. A point source of ^{125}I was therefore placed in a water-filled tank and the detector was placed at the very surface of the water (Figure 1). The ability of the equipment to detect ^{125}I at different points in a plane through the central axis of the detector was measured.

Experimental Procedure in Vivo

The fibrinogen was labeled according to the iodine-monochloride method of McFarlane¹⁴ and was kindly provided by Dr. Thorell of the Department

of nuclear medicine, Malmö. The clotability of the fibrinogen was found to be around 92%.

The measurements were made in 36 consecutive patients undergoing operation for uterine prolapse. Patients with thyroid disease were excluded. All patients were older than 50, and the average age was 66. They were all operated on in the lithotomy position.

The day before the operation the thyroid was blocked by 0.3 g of potassium iodide by mouth. The same amount was given every day for 14 days after the operation. On the evening before the operation, $100\ \mu\text{Ci}\ ^{125}\text{I}$ -fibrinogen was injected intravenously. The first measurement was made the following day, immediately before the operation, and again on days 3, 5, and 7. The recordings were made with the patient supine and with her legs raised 45° .

The following measuring areas were used on both limbs: *on the lower limb* we measured five areas equally distributed about 5 cm apart between the medial malleolus and the lower part of the medial femoral epicondyle; *in the popliteal area*, only one area was used; *on the thigh*, we used 4 areas about 5 cm apart starting from the upper part of the medial femoral epicondyle and extending in a proximal direction along the main vessels.

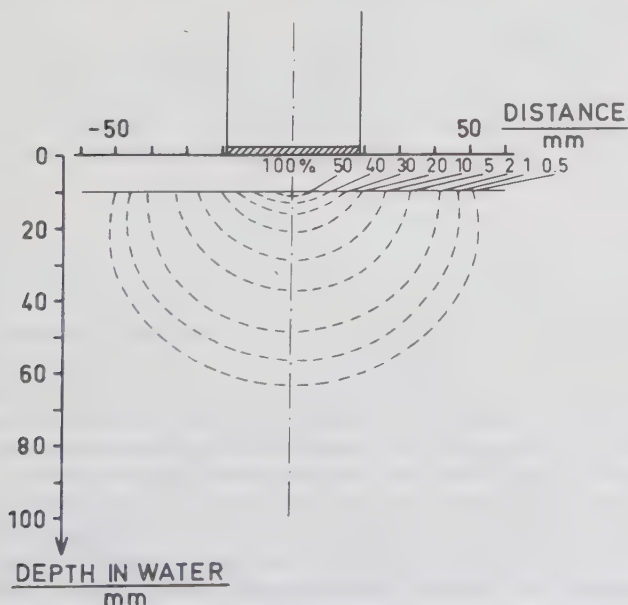


FIG. 1. Relative isosensitivity lines for point sources of ^{125}I in water. The sensitivity when the source was placed centrally on the detector surface was set to 100.

The detector was gently pressed against the skin with its central axis perpendicular to the skin surface. The recording time in each area varied between 30 and 120 seconds so that the number of counts always exceeded 1,000 per area. The number of counts over the heart varied between 5,000 and 20,000.

The point over the heart that gave the highest count rate was chosen as reference. The count rate in any measuring area on the lower limb was expressed in relation to the count rate over the heart. The figure so obtained was referred to as the "percentage count rate," analogous to "percentage uptake" described by Negus et al.¹³

Radiation Dosimetry

The activity of the ^{125}I injected was, as mentioned, 100 μCi per patient. The effective half-life of the injected activity, as determined from measurements in blood samples from 30 of our patients was 3.7 days (± 0.7 SD). The minimum and maximum values recorded were 2.8 and 5.2 days respectively. Assuming that 70% of the whole body content of ^{125}I is present in blood, the cumulated activity of ^{125}I should be, on the average, 530 μCi day. If ^{125}I is evenly distributed in the total blood volume of the adult, the absorbed dose per activity unit will be $9 \mu\text{rad} \cdot \text{h}^{-1} \cdot \mu\text{Ci}^{-1}$.¹⁴ For our patients, the absorbed dose in the blood was thus around 80 mrad (60–110 mrad).

The absorbed dose to other tissues and organs, except the thyroid, is considerably lower. If the thyroid uptake of iodine is assumed to be 1% (due to the blocking), and if all the ^{125}I activity injected gradually becomes available for thyroid uptake, the absorbed dose to the thyroid will be 2–3 rad.

Results and Discussion

In vitro

Figures 1 and 2 show the relative sensitivity of the detector for ^{125}I at different depths in a water phantom. The count rate was normalized to 100 when the ^{125}I point source was placed at the surface of the detector. At a depth of 1 cm in water, the relative sensitivity along the central axis decreased from 100 to 50. At a depth 2.5 cm it fell to 14, and at 4 cm it dropped to 4. As Figures 1 and 2 show, the possibility of detecting small fibrin deposits, decreases very quickly with increasing depth of the tissues.

The marked variation of the sensitivity at different depths is due mainly to the fact that the solid angle under which the detector records the radioactivity varies markedly with the depth just in front of the detector. The pronounced attenuation of the low energetic photon radiation is here of minor importance. With knowledge of the field of view of the detector, it was

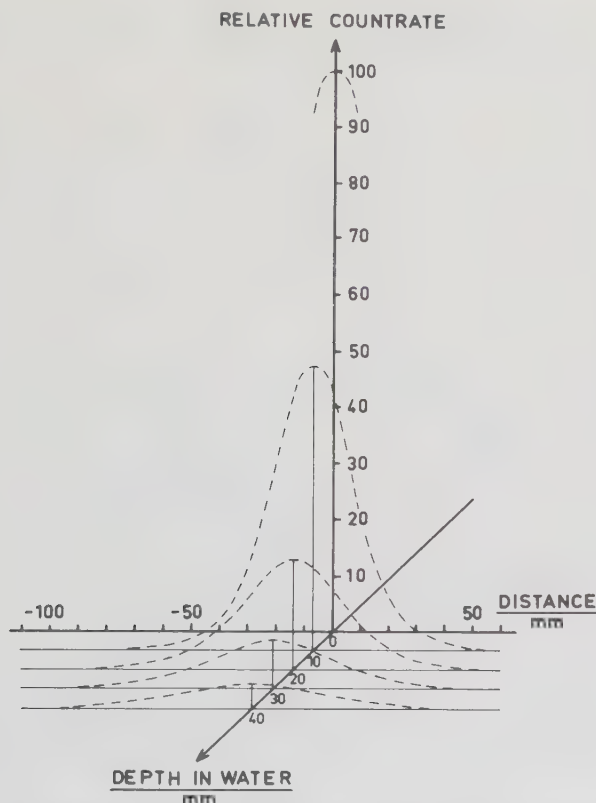


FIG. 2. Relative detector sensitivity of a point source of ^{125}I as a function of distance from the central line of the detector and for various depths (10, 20, 30 and 40 mm) in water.

decided that the distance between the two measured areas should be 5 cm (Figure 3).

It is obvious that one of the most important disadvantages of this technique is its poor ability to detect deep thrombosis. One way of diminishing the above mentioned variation with depth would be to increase the distance between the detector and the skin. However, this would in turn increase the statistical uncertainty of the recordings in all parts of the volume examined. This would be unacceptable since the desired maximal injected activity is $100\ \mu\text{Ci}$ per patient, and even now the statistical uncertainty contributes substantially to the overall uncertainty of the recording, if the recording time

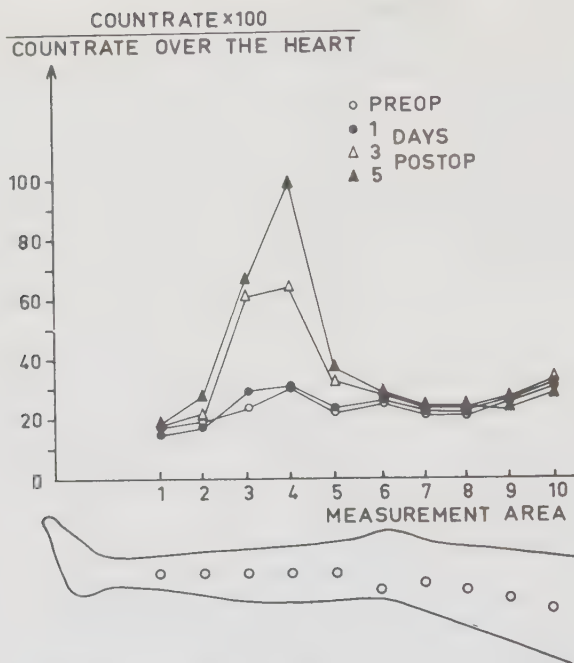


FIG. 3. Measurements in a patient who developed thrombosis of the posterior tibial vein. The measurements were made at the indicated position every other day up to a week after the surgery. Count rates over the different measurement areas are expressed in relation to the count rate over the heart.

is not to be unacceptably long. If, on the other hand, $^{99}\text{Tc}^{\text{m}}$ -marked plasmin or streptokinase is utilized, a higher activity could be given and the distance between the detector and the skin could be increased.^{15,16} The main disadvantage of the $^{99}\text{Tc}^{\text{m}}$ -marked compounds is that their physical half-life is short and will therefore not permit recordings over several days.

In vivo

To investigate the uncertainty of a single measurement *in vivo*, an additional experiment was carried out. Thirty recordings were repeated over the same area in three different areas in each of three patients. The detector was removed and replaced between consecutive measurements, and the standard deviation of the recordings at each site of measurement was calculated.

Table 1 lists the mean value of individual standard deviations in 3 patients.

Based on knowledge of the counting statistics, the residual contribution to the overall uncertainty was estimated according to the following formula:

$$(\text{SD})_o^2 = (\text{SD})_{st}^2 + (\text{SD})_{re}^2$$

where o = overall, st = statistic, and re = residual. Table 1 shows that the recordings in the popliteal area are less certain than those over the calf and the heart. It also shows that the counting statistics contributes substantially to the overall uncertainty if the number of counts is below 1000.

To assess the uncertainty of the day-to-day variation of the "percentage count rate," the standard deviations of percentage count rate values obtained on 7 consecutive days at each measurement site were calculated. Twenty patients without signs of thrombosis were selected. Most of the patients had varicose veins. The means of the individual standard deviations in the 20 patients were calculated (Table 2). The mean standard deviation in the calf was $\pm 2.0\%$ of the count rate over the heart, in the popliteal area $\pm 2.7\%$, and in the thigh $\pm 2.6\%$. This low day-to-day variation means that the probability of an increase of more than 5% of the count rate over the heart on two consecutive days is less than 1%.

Of 36 patients studied, 9 had an increase in percentage count rate of more than 5% on 2 consecutive days compared with the preoperative value. In 2 of these patients arthritis was the cause. The remaining patients (20%) were considered to have thrombosis. All of them had an increase in percentage count rate in the calf. In 2 patients an extension into the popliteal and

TABLE 1
Components of the Overall Uncertainty of a Single Measurement Over Three Different Areas

Measurement Area	Overall Uncertainty (SD %)	Counting Statistics (SD %)	Residual Uncertainty (SD %)
Calf	± 3.1	± 2.5	± 1.6
Popliteal area	± 5.4	± 2.2	± 4.8
Heart	± 2.4	± 1.7	± 1.4

Mean values of relative standard deviation were calculated from 30 repeated simultaneous measurements in 3 patients.

TABLE 2
Mean Value and Overall Standard Deviation of Day-to-Day Measurements Over Three Different Areas in 20 Normal Patients

Measurement Area	Count Rate Relative to Heart	
	Mean	$\pm$ SD
Calf	19%	$\pm 2.0\%$
Popliteal area	26%	$\pm 2.7\%$
Thigh	29%	$\pm 2.6\%$

The mean values of individual standard deviations are given.

femoral veins was found. Phlebography confirmed the diagnosis, and the patients received antithrombotic treatment. Figure 3 shows the measurements of a patient with a thrombus occluding the posterior tibial vein. The increase in percentage count rate is substantial and typical for a fibrin deposit big enough to be detected by phlebography.

Summary

Most postoperative thrombi are initiated during the operation. Early thrombosis of the lower limbs is often asymptomatic. Therefore most patients leave the hospital untreated, and since symptoms may not develop for several weeks, there could be a serious delay in diagnosis.

There is no such thing as 100% effective prophylaxis against thrombosis. Both dextran and heparin in small doses have a good effect, but have side effects. We therefore believe that proper postoperative screening should be most useful for all "high-risk patients," not only for scientific reasons, but also from a clinical point of view. The ¹²⁵I-fibrinogen method, as we have evaluated and adopted it, seems to be a realistic screening method for detecting early thrombosis.

Several authors have proposed that an increase in percentage count rate varying between 10 and 20% should be used as a criterion of thrombosis.^{3,13,17} With the equipment used in this study, under optimal conditions an increase of 5% on 2 consecutive days would be a sufficient criterion. But for routine clinical use, we suggest that an increase of more than 10% on 2 consecutive days compared with preoperative value should be regarded as a positive sign of thrombosis.

We stress the importance of comparing the preoperative value, and also of not relying too much on any difference between the two legs, since there are normal anatomic differences between the two limbs.^{17,18} If such a comparison, with the preoperative recording is always made and the legs are raised 45°, it should minimize the number of false-positive diagnoses caused by varicose veins.

The greatest source of error in the ¹²⁵I-fibrinogen method lies in the recording technique. Most commercially available equipment used for ¹²⁵I-fibrinogen detection is still based on a rate meter. Equipment based on a scaler-timer, however, reduces the uncertainty of the recordings and offers the possibility of estimating the statistical uncertainty.¹⁹ However, it is necessary to check its sensitivity every day with the same source of ¹²⁵I.

*Kurt Bernstein, M.B.B.S., F.I.C.A.
Consultant Anaesthetist
Department of Anaesthesiology 2
University Hospital of Malmö
214 01 Malmö, Sweden*

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References

1. Flanc, C., Kakkar, V.V., Clarke, M.B.: The detection of venous thrombosis of the legs using ¹²⁵I-labelled fibrinogen. *Br. J. Surg.*, 55: 742, 1968.
2. Kakkar, V.V., Howe, C.T., Flanc, C., et al.: Natural history of postoperative deep-vein thrombosis. *Lancet*, 2: 230, 1969.
3. Kakkar, V.V.: The ¹²⁵I-labelled fibrinogen test and phlebography in the diagnosis of deep vein thrombosis. *Millbank Mem. Fund. Q.*, 50: 206, 1972.
4. Haeger, K.: Den kliniska trombosdiagnosens (o) tillförlitlighet. *Läkartidningen*, 62: 1067, 1965.
5. Kaij, K.: Tromboembolifrekvensen i ett obduktionsmaterial. *Läkartidningen*, 56: 1437, 1965.
6. Linell, F.: Heparinsymposium. Jönköping, 1965.
7. Björnberg, Ö.: Dödande lungemboli hos gamla patienter med intermedicinska sjukdomar. *Nord. Med.*, 68: 1548, 1964.
8. Ambrus, J.L., Ambrus, C.M., Back, M., et al.: Radio-labelled thrombi. *Ann. N.Y. Acad. Sci.*, 68: 97, 1957.
9. Hobb, J.T., Davies, J.W.L.: Detection of venous thrombosis with ¹³¹I-labelled fibrinogen in the rabbit. *Lancet*, 2: 134, 1960.
10. Palko, P.D., Nansen, E.M., Fedoruk, S.O.: The early detection of deep vein thrombosis using ¹³¹I-tagged human fibrinogen. *Can. J. Surg.*, 7: 215, 1965.
11. Atkins, P., Hawkins, L.A.: Detection of venous thrombosis in the legs. *Lancet*, 2: 1217, 1965.
12. McFarlane, A.S.: Labelling of plasma proteins with radioactive iodine. *Biochem. J.*, 62: 135, 1956.
13. Negus, D., Pinto, D.J., Le Quesne, L.P., et al.: ¹²⁵I-labelled fibrinogen in the diagnosis of deep vein thrombosis and its correlation with phlebography. *Br. J. Surg.*, 55: 835, 1968.
14. McEwan, A.C.: Dosimetry of radionuclides in blood. *Br. J. Radiol.*, 47: 652, 1974.
15. Persson, B.R.R., Darte, L.: Labelling plasmin with technetium-99m for scintigraphic localization of thrombi. *Int. J. Appl. Radiat. Isot.* 28: 97, 1977.
16. Darte, L., Olsson, C.G., Persson, B.R.R.: ⁹⁹Tc^m-labelling of streptokinase and its use for detection of deep vein thrombosis using scintillation camera or hand detector. *Proceedings of the XIII International Annual Meeting of the Society of Nuclear Medicine*, Copenhagen, 1975.
17. Becker, J.: The diagnosis of venous thrombosis in the legs using ¹²⁵I-labelled fibrinogen. *Acta Chir. Scand.*, 138: 667, 1972.
18. Pollack, E.W., Werber, M.M., Vicitry, W.: Fibrinogen uptake test. Criteria for interpretation of results in patients with venous thrombosis. *Am. Surg.*, 43: 119, 1977.
19. Forsberg, K.: ¹²⁵I-fibrinogen in the diagnosis of deep vein thrombosis. *Br. Med. J.*, 4: 286, 1975.

A method for determination of the depth of thrombi after injection of fibrinogen labelled with iodine 125

By L. Jacobsson, Ph.D., and S. Mattsson, Ph.D.*

Department of Radiation Physics

K. Bernstein, M.D., U. Ulmsten, M.D., and B. Åstedt, M.D.

Department of Obstetrics and Gynaecology,
Malmö General Hospital,
University of Lund, S-21401 Malmö, Sweden

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ABSTRACT

By using a specific characteristic of ^{125}I decay, the depth of thrombi located in the lower limb could be determined. Twelve thrombi in nine patients were studied with the method and their localization was in all cases confirmed by phlebography and clinical examination. The results of the phlebograms were in good agreement with those of the ^{125}I -fibrinogen method. The present method offers a promising alternative to phlebography in the diagnosis of postoperative thrombosis.

The conventional method of detecting thrombi with ^{125}I -fibrinogen gives no information about the depth at which the radioactive tracer is located. With this method it is therefore not possible to differentiate between the fibrinogen uptake of thrombosis in deep and superficial veins. Superficial vein thrombosis may partly explain the 20% "false positive" findings reported in studies comparing the ^{125}I -fibrinogen method with phlebography (Gallus, 1975; Pollack *et al.*, 1977). If a reliable determination of the depth of the ^{125}I activity could be made, this would considerably increase the diagnostic value of the ^{125}I -fibrinogen method.

We present here a new method for determination of the depth of thrombi based on the conventional ^{125}I -fibrinogen method and preliminary clinical results obtained by using it.

METHOD OF DEPTH MEASUREMENT

The new method for depth measurement is based on a specific characteristic of the decay of ^{125}I which proceeds via electron capture, EC, to an excited level in ^{125}Te (Fig. 1). In this transition, on the average 0.74 K X rays per disintegration are emitted. De-excitation of the excited level occurs mainly via internal conversion, IC, which gives on the average 0.67 K X-rays per disintegration. A minor part (7%) of the de-excitation occurs via γ -emission. The energies of the X rays vary from

27 keV to 31 keV with a weighted mean value of 28 keV. The energy of the γ photons is 35 keV.

In about half of the disintegrations, a photon is emitted both during electron capture and in de-excitation. The mean number of such events per disintegration is given by the product $0.74 \times (0.67 + 0.07) = 0.54$. The two X-ray photons or alternatively one X-ray and one γ -photon are emitted almost simultaneously with no correlation in their directions.

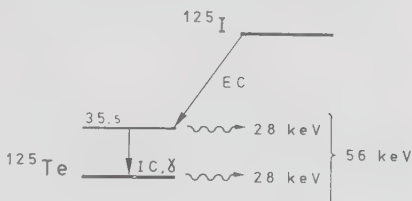


FIG. 1.

Decay scheme for ^{125}I . In both the electron capture (EC) and internal conversion (IC) transitions, K X rays can be emitted from Te. There is a possibility of emission of two coincident K X rays.

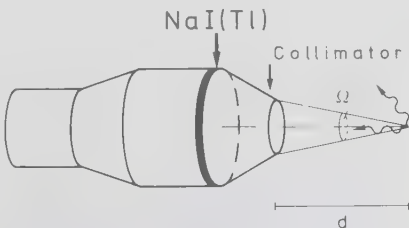


FIG. 2.

Geometry for determination of the depth of a ^{125}I -source. Ω denotes the solid angle and d the distance between the collimator and the source.

Dedicated to the memory of Curt Pettersson, Ph.D.

*Present address: Radiation Physics Department, University of Lund, S-221 85 Lund, Sweden.

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The probability of detecting both the coincident photons depends on the solid angle of the detector and on the attenuation in the material between the detector and the ^{125}I (Fig. 2). The number of coincident photons detected, N_c , is given by

$$N_c = 0.54 A t \left(\frac{\Omega}{4\pi} e^{-\mu d} \right)^2 \epsilon^2 \dots (1)$$

A = activity of ^{125}I .

t = time of measurement

Ω = solid angle

μ = effective attenuation coefficient.

d = mean distance between the collimator and the ^{125}I source.

ϵ = efficiency of the detector.

In the pulse-height distribution from a NaI (Tl)-detector coincident registrations are seen as a distribution at about 56 keV. This distribution is clearly distinguishable from the distribution of single 27–35 keV photons (Fig. 3). The present measurements were made using a NaI(Tl)-detector with diameter 124 mm and thickness 1.5 mm. The detector was fitted with a brass collimator having a length of 50 mm, an opening diameter of 40 mm and a thickness of 5 mm. The detector pulses were analysed by a 512 channel analyser and the number of counts, N , in the energy interval 9–40 keV and N_c , in the interval 44–70 keV were summed.

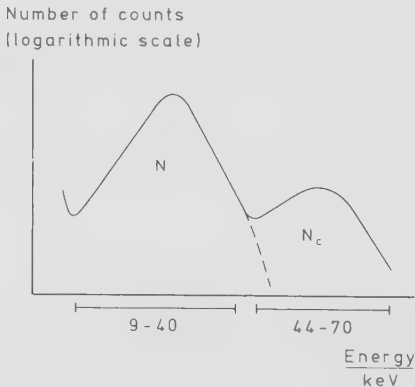


FIG. 3.

The pulse-height distribution from ^{125}I recorded by a 124 mm diameter $\times$ 1.5 mm NaI(Tl)-detector. Single photons are recorded in the energy interval 9–40 keV and two coincident photons in the interval 44–70 keV. N and N_c denote the numbers of counts in the respective energy intervals.

The quotient between the number of coincident registrations, N_c , and the total number of photons registered, N_t , is given by

$$\frac{N_c}{N_t} = \frac{0.54}{1.47} \frac{\left(\frac{\Omega}{4\pi} e^{-\mu d} \epsilon \right)^2}{\frac{\Omega}{4\pi} e^{-\mu d} \epsilon} = 0.37 \frac{\Omega}{4\pi} e^{-\mu d} \epsilon \dots (2)$$

where N_t is equal to $N + 2N_c$.

This formula is valid when the activity is so small that the number of random coincident registrations can be neglected (see below).

With a knowledge of the solid angle, the effective attenuation coefficient and the detector efficiency, the distance to the radiation source can be calculated from the quotient N_c/N_t using equation (2). An easier and more reliable way is to use an experimentally-determined relation between N_c/N_t and depth. Fig. 4 shows such a relation determined for a point source at different depths in a water phantom (curve a).

Since the attenuation coefficient for muscle is almost the same as for water, the relation N_c/N_t versus depth in water can be used for determination of the depth of ^{125}I -fibrinogen uptake in a thrombus. If the uptake cannot be considered as a point source, the above relation is not exactly valid. When the

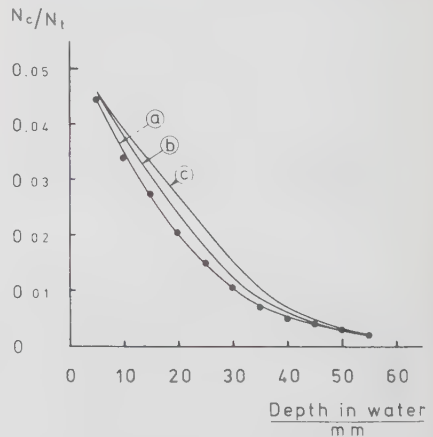


FIG. 4.

The ratio N_c/N_t for a ^{125}I source placed at different depths in water: (a) point source, (b) linear sources, $L=50$ mm, (c) linear sources, $L=100$ mm.

uptake can be considered as being a line source with length L , formula (2) is replaced by

$$\frac{N_c}{N_t} = 0.37 \frac{\int_0^L \left(\frac{\Omega}{4\pi} e^{-\mu d} \epsilon \right)^2 dl}{\int_0^L \frac{\Omega}{4\pi} e^{-\mu d} \epsilon dl} \dots (3)$$

Using this formula, the correction to the relation between N_c/N_t and the depth in water has been calculated for line sources of different lengths (Fig. 4, curves b and c). The differences between depths calculated from curves a, b, and c are always less than 6 mm. For linear sources up to 30 mm long, curve (a) can be used.

Figure 5 shows a cross-section of the lower limb just beneath the knee. Measured from the medial side, the deep veins of the calf are located at depths of about 60 mm, the superficial veins at depths of 0–10 mm and the veins of the muscles approximately halfway between the superficial and deep veins. If these anatomical facts are considered together with the results of the phantom measurements mentioned above, we can see that the ratio N_c/N_t for a thrombus in a deep vein differs from that in a superficial vein by a factor of 30–50.

CLINICAL APPLICATIONS

The technique described was applied to nine patients with a mean age of 68 years (range 52–86 years). They had all received surgery for uterine prolapse or carcinoma of the uterus or the ovaries. On the day before operation, 3.7 MBq (100 μ Ci) 125 I-fibrinogen was injected. With a hand-held detector, the count rates over predetermined areas on both legs were recorded in accordance with a special scheme described previously (Bernstein *et al.*, 1979). The recordings were repeated on the 3rd, 5th and 7th postoperative days. When an increased uptake of 125 I was found in any of the areas under investigation, a determination of the depth of the radioactive tracer was made as follows: The patient was placed in a room shielded from background radiation in a supine position with the legs raised at 45 deg. The number of counts over the area of increased 125 I-uptake was recorded for 100 seconds and the number of counts registered over the same area on the other leg was subtracted. Usually, the measurements were made from the medial side of the lower limb. Sometimes, however, complementary measurements were also made from the posterior side of the lower limb. Phlebography was performed

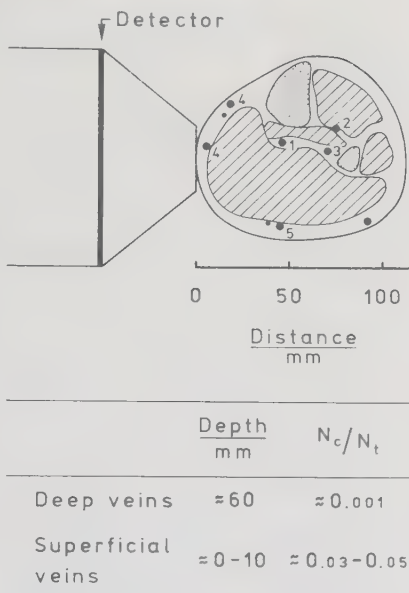


FIG. 5.

Schematic cross section of the proximal part of the calf. The positions of the major veins are indicated by the following numbers: (1) the posterior tibial vein, (2) the anterior tibial vein, (3) the fibular vein, (4) the major saphenous vein and (5) the minor saphenous vein. The table shows approximate depths for the superficial and deep veins as well as typical values for the ratio N_c/N_t for thrombi in superficial and deep veins.

in all patients. In two women in whom the occurrence of postoperative thrombosis was already known and phlebographically verified, 125 I-fibrinogen was injected and measurements of the depth of the thrombus were made the next day.

RESULTS

So far, twelve thrombi in nine patients have been detected with the present method. All thrombi except one have also been verified phlebographically (Table I). In the only case for which the thrombosis could not be seen using X rays, the depth given by the method suggested a superficial thrombosis, which was also clinically evident. In all the other cases, the depth of the thrombosis as measured by the 125 I-method corresponded almost exactly to the

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TABLE I

DEPTH OF THROMBUS IN MM FROM THE MEDIAL SIDE OF THE CALF, MEASURED USING THE ^{125}I -FIBRINOGEN METHOD

Phlebographic localization of the thrombus	Patient number								
	1	2	3	4	5	6	7	8	9
Femoral vein						> 48			
Posterior tibial vein	38 (34-45)					38 (34-45)			
Fibular vein			> 52	31 (28-37)*					
Muscle veins of the calf		27 (23-31)		31 (28-37)*	50 (40-70)		27 (24-30)	23 (20-26)	30 (29-31)
Superficial thrombosis						7			

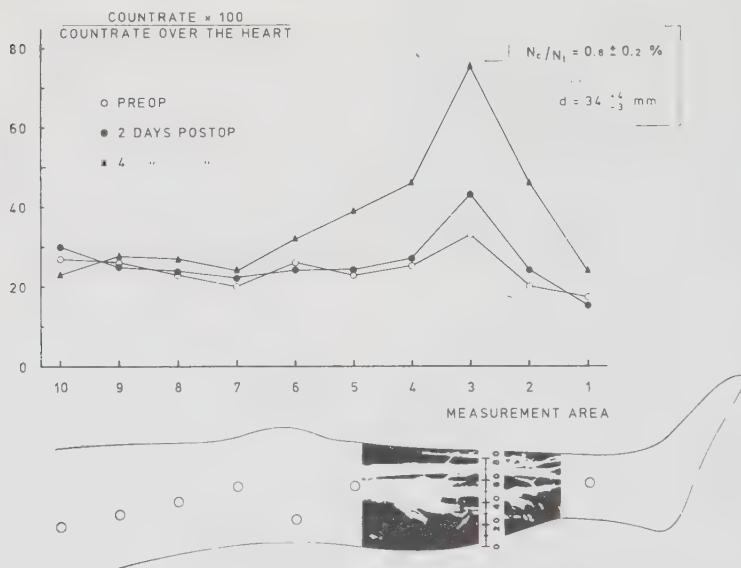
*Registered as a single thrombus by the ^{125}I -coincidence method.

FIG. 6.

Extensive thrombus in the posterior tibial vein in patient No 1. The upper part of the figure illustrates how the position of the thrombus has been determined by the conventional ^{125}I -fibrinogen test. With the aid of the new ^{125}I -coincidence method, the depth of the thrombus has been measured from the posterior side of the calf to be (34 ± 4) mm. The lower part of the figure shows the phlebographic picture. From this, the depth of the thrombus was estimated to be between 30 and 35 mm from the posterior side of the calf.

localization of the thrombosis measured at phlebography (see also Fig. 6).

In the calf, the average depth to thrombi of the deep veins was 44 mm and to thrombi of the muscle veins 31 mm from the medial side (Table I). The

deepest thrombus detected in the present investigation was located more than 50 mm from the medial side of the calf and the most superficial only 7 mm from the skin surface.

Figure 7 gives the uncertainty in the depth

localization of thrombi for various times of measurements. The curves are calculated for a typical value of the count rate in the 28 keV peak, 50 cps, and for a typical background count rate, 1 cps, in the coincidence peak. Deep-lying thrombi require prolonged measurement times to give the same accuracy of localization as superficial thrombi.

The influence of random coincidences on the depth determination was found to be negligible at normal count rates of 50 cps in the 28 keV peak. At the maximal count rate found over a thrombus, 250 cps, the method gives a depth value which is within 3% of the true value.

DISCUSSION

The accuracy of the ^{125}I -method (Fig. 7) depends mainly on the number of counts registered in the coincidence peak after subtraction of background. It is evident from Fig. 7 that long measurement times are needed, particularly for the localization of the deep thrombi. Furthermore, accurate determi-

nations of deep thrombi cannot be made if the background count rate is too high. This can partly be compensated for by a further increase in the recording time.

In the only case where the findings from phlebography and the ^{125}I -coincidence method differed, two thrombi were found in the same calf. One thrombus was located in one of the deep veins and the other in a muscle vein. The larger part of the photons recorded by the detector probably originated from the most superficial thrombus in the muscle vein, but no sure determination of the depth of the individual thrombi could be obtained.

Apart from differentiating between superficial and deep thrombi, the present method can also be used to permit the early localization of thrombi detected by conventional ^{125}I -fibrinogen screening. By thoroughly measuring the depth of a thrombus, its ^{125}I -activity can be estimated from the values of the count rates.

If the ratio of ^{125}I -fibrinogen to the fibrinogen in the blood is known, the amount of fibrinogen in the thrombus can be calculated. This facilitates evaluation of the size of the thrombus since the count rate is highly dependent on its depth.

The recordings can easily be repeated with good reproducibility, making it possible to follow the spontaneous development of a thrombosis and the effect of the chosen treatment. Since we have shown that localization of thrombi can be performed to a depth greater than 50 mm, the method is not restricted only to measurements on limbs.

It is evident that the present method is potentially of great clinical value. Even if the number of patients studied so far is rather small, there was in all cases good agreement between the depths of thrombi found by this method and those found by phlebography. For the investigator, the present ^{125}I -coincidence method provides an easily-handled technique. In addition, it is well tolerated by the patients. We, therefore, believe that the present method offers a promising alternative to phlebography.

REFERENCES

- BERNSTEIN, K., MATTSSON, S., ULMSTEN, U. and ÅSTEDT, B., 1979. The ^{125}I -fibrinogen method for early diagnosis of venous thrombosis. *Vascular Surgery*, **13**, 33.
 GALLUS, A. S., 1975. ^{125}I -fibrinogen leg scanning. In *Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism* (Ed. J. Frattoloni and S. Wessler), pp. 77-99. (National Institute of Health, Bethesda, U.S.A.).
 POLLACK, E. W., WEBER, M. M. and VICTERY, W., 1977. Fibrinogen uptake test. Criteria for interpretation of results in patients with venous thrombosis. *American Surgery*, **43**, 119.

Uncertainty in depth (S.D.)
mm

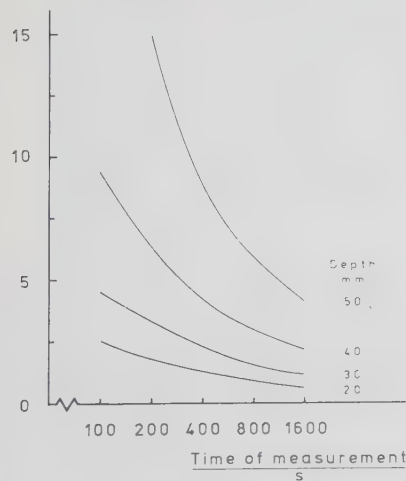


FIG. 7.

The statistical uncertainty (one standard deviation) in the depth determination. The curves are calculated for a typical value of the count rate in the 28 keV peak, 50 cps, and for a typical background count rate, 1 cps, in the coincidence peak.

Incidence of Thrombosis After Gynecologic Surgery Evaluated by an Improved ^{125}I -Fibrinogen Uptake Test

Kurt Bernstein, M.B.B.S., F.I.C.A., Ulf Ulmsten, M.D., F.I.C.A.,
Birger Åstedt, M.D., F.I.C.A., Lars Jacobsson, Ph.D., F.I.C.A., and
Sören Mattsson, Ph.D., F.I.C.A.

MALMÖ, SWEDEN

Abstract

Two hundred and seventy-six women over 50 years of age who had gynecologic surgery were followed postoperatively with the ^{125}I -fibrinogen uptake test (^{125}I -FUT) to detect deep venous thrombosis (DVT). By using a newly devised technique based on conventional ^{125}I -FUT, the exact depth of thrombi could be determined. The correlation between the results with our new technique and those from phlebography was almost 100%. Forty-seven (17%) of the women developed DVT postoperatively, 60% of them occurring in the calf muscle veins. Patients subjected to abdominal hysterectomies for malignant diseases had the highest incidence of DVT (36%), whereas those operated on for benign diseases with the same technique had the lowest (11%). Patients operated on for uterine prolapse had an intermediate DVT frequency of 15% but advanced age and estrogens given preoperatively increased the frequency. Neither the type of anesthesia (epidural or general), nor the duration of the operation, significantly influence the incidence of DVT in this study.

Introduction

Deep vein thrombosis (DVT) in legs causing pulmonary embolism is one of the most frequent causes of death after gynecologic surgery. In addition, it is also a major factor of mortality in child birth. Since clinical evaluation is an uncertain method, objective tests are necessary for proper diagnosis and prompt treatment of the condition. Several methods of diagnosing DVT are available, but usually the ^{125}I -fibrinogen uptake test (FUT) is used as a routine screening procedure to investigate patients at high risk of developing thrombotic processes after surgery.

Previously, we evaluated a ^{125}I -FUT for DVT detection both in vitro and in vivo.¹ After some modifications of the standard test, it was possible to increase its sensitivity and accuracy. Furthermore, taking advantage of the special decay scheme of ^{125}I , we were recently able to elaborate a new technique for deter-

From the Departments of Anaesthesia, Obstetrics, and Gynecology, and Radiation Physics, Malmö General Hospital, University of Lund, Malmö, Sweden.

mining the depth and extension of DVT in the legs.² This new technique, the ¹²⁵I-fibrinogen single detector sum coincidence method, which has been described in detail elsewhere,² proved to be more sensitive than routine examination of phlebographic films in detecting small thrombi of the lower limbs.

The aim of the present work was to study the incidence of thrombi in a high-risk group of women after gynecologic surgery using the improved ¹²⁵I-FUT in combination with the ¹²⁵I-fibrinogen sum coincidence technique.

Materials and Methods

We studied 276 consecutive patients, each more than 50 years old, admitted to the Department of Obstetrics and Gynecology between February 1977 and May 1979 for elective gynecologic surgery. Their mean age was 64 years (range 50–86), and their mean weight was 67 kg (range 47–130).

As Table 1 shows most patients were operated on because of uterine prolapse. The type of anesthesia (epidural or general) varied in the prolapse group, whereas all patients in the abdominal laparotomy group had general anesthesia. The diagnoses of the patients were registered, as were the durations of the operations, previous DVTs, and presence of varicose veins. It was also noted whether patients were treated preoperatively with estrogens. Patients with thyroid disease were excluded from the study.

In addition to the conventional treatment to avoid postoperative thrombosis (early mobilization and phyiotherapy), the patients on whom laparotomies had been performed were given extra prophylaxis. Forty-five patients received dextran (Macrodex), 500 ml IV, on the day of operation, starting at the beginning of the operation. They were also given 500 ml IV on the first postoperative day. This procedure has been used as an antithrombotic routine after surgery in our

TABLE 1
Indications for Surgery, and Possible Factors Influencing the Frequency of DVT

	No. of Patients	
Uterine prolapses (vaginal plasty)	190	
Abdominal hysterectomies	86	
Benign diseases		47
Malignant diseases		39
Without metastatic carcinoma		25
With metastatic carcinoma		14
Total	276	
Previous DVT		30
Varicose veins		170
Epidurals (prolapses)		86
General anesthesia		190
Prophylaxis with DHE		40
Prophylaxis with dextran		45
Patients on estrogens preoperatively		31

department for several years. Another group of 40 patients received dihydroergotamin (DHE) (Orstanorm), 0.5 mg $\times$ 2 IM, for 7 days postoperatively, the first dose was given IV at the onset of anesthesia.

Diagnosis of Leg Vein Thrombosis. Fibrinogen was labeled with ^{125}I using the iodine monochloride method.³ The clotability was found to be about 92%. The day before operation and for 15 days after it, the thyroid was blocked by giving the patient 0.3 g of potassium iodide daily by mouth. On the evening of the day before the operation, 3.7 MBq of ^{125}I -fibrinogen was injected IV into the patients.

The first recording was made immediately before the operation, then repeated on days 1, 3, 5, and 7 postoperatively, according to a procedure described elsewhere.¹ The count rate in any area of measurement on the lower limb was expressed as a percentage of the count rate of heart, as described by Negus et al.⁴

The technique used to register the amount of radiation has been described elsewhere.¹ The recordings were carried out with a scintillation detector (Eberlein MS-2F, Eberlein Instrument Corporation, Santa Fe). Its detector is a 1 mm thick NaI (Tl) crystal 38 mm in diameter. It has a 0.025 mm thick aluminium window shielded from the side by 2.8 mm of Al. The energy window of the single-channel analyzer was set at 28 ± 7 keV. The sensitivity of the equipment was checked daily before and after the measurements.¹

To determine the depth of thrombi, the newly devised ^{125}I -fibrinogen sum coincidence technique was used. Since it has been described in detail elsewhere,² it is only briefly outlined here:

The decay scheme of ^{125}I is unique. The radionuclide decays by electron capture (EC) (100%) followed by 35 keV γ emission (7%), or by internal conversion (IC). The energies of the K x-rays emitted during electron capture and internal conversion vary from 27 keV to 31 keV, with a weighted mean value of 28 keV. At the EC, on the average, 0.74 K x-rays are emitted per disintegration, and at the IC, as a mean, 0.67 K x-rays are emitted per disintegration.

In about half of the disintegrations, a photon is emitted during both electron capture and internal conversion. Two x-ray photons are then emitted almost simultaneously without any directional correlation. By a single detector these coincidence photons are registered together in the energy interval 44 to 70 keV. By taking the ratio between the number of coincident photons registered and the total number of photons recorded, one gets a parameter, which is very sensitive to the distance between the detector and source of emission.²

For the present depth determinations we used a detector with a 124 mm diameter and 1.5 mm thick NaI (Tl) crystal. It was equipped with a brass collimator with a length of 50 mm, an opening diameter of 40 mm, and a thickness of 5 mm. The measurements were carried out in a low background room.

Phlebography was performed according to the technique described by Nylander.⁵

Clinical Application. The ^{125}I -FUT was interpreted as positive if the count rate in any measuring area was increased postoperatively by at least 10% units compared to the preoperative value, and if the rise persisted for 2 days or more.¹ If the test was positive, screening was continued daily. Clinical signs of thrombosis or pulmonary embolism were looked for until the patient left the ward. If there was any clinical sign of pulmonary embolus, a lung scintigram was performed.

The first 27 patients with positive FUTs had phlebographies performed on clinical grounds only. The last 24 patients with positive FUTs were investigated with both the ^{125}I -fibrinogen sum coincidence method and phlebography to study the correlation between the two tests.

Results

There were 61 thrombi in 51 patients, and Figure 1 shows their location. Four patients had *only* superficial venous thrombosis. This means that 47 (17%) had DVT. Ten percent of the thrombi were located in the femoral and/or popliteal veins; 20% in tibial or fibular veins; 60% in calf muscle veins; and 10% in superficial veins. Eight patients had multiple thrombi.

In the last 24 patients with positive FUT, the depths and exact location of the thrombi were determined by the ^{125}I -fibrinogen sum coincidence technique. All together, these 24 patients had 28 thrombi.

There were two main groups of thrombi—one with depths <10 mm and the other with depths >10 mm from the skin surface. Of the 28 thrombi, 22 were studied with phlebography, and a very good agreement was found between the depths of thrombi as determined by the ^{125}I -fibrinogen sum coincidence technique and by phlebography. In 11 patients in whom the depths of thrombi could be measured accurately on the x-ray films, an almost exact correlation was found between the two techniques (Figure 2). One thrombus was localized at a considerable depth (more than 48 mm) in the thigh, and when the x-ray film was studied retrospectively, a thrombus was found protruding from the deep femoral vein into the superficial femoral vein.

The total incidence of DVT in the present study was 17%. As Table 2 shows, hysterectomies for benign diseases had the lowest rate of DVT (11%), whereas hysterectomies for malignant diseases had the highest (36%). The difference is statistically significant, ($P < 0.02$). Patients operated on for uterine prolapse were intermediate in DVT frequency (15%). In patients operated on for prolapse, there was no difference in the incidence of DVT between those with epidural and those who had general anesthesia.

The duration of the operation also seemed to play a minor role in the development of postoperative thrombosis: Patients operated on for less than 100 minutes had an incidence of thrombosis of 15%, whereas the corresponding figure for those operated on for more than 100 minutes was 21%. The difference was not significant.

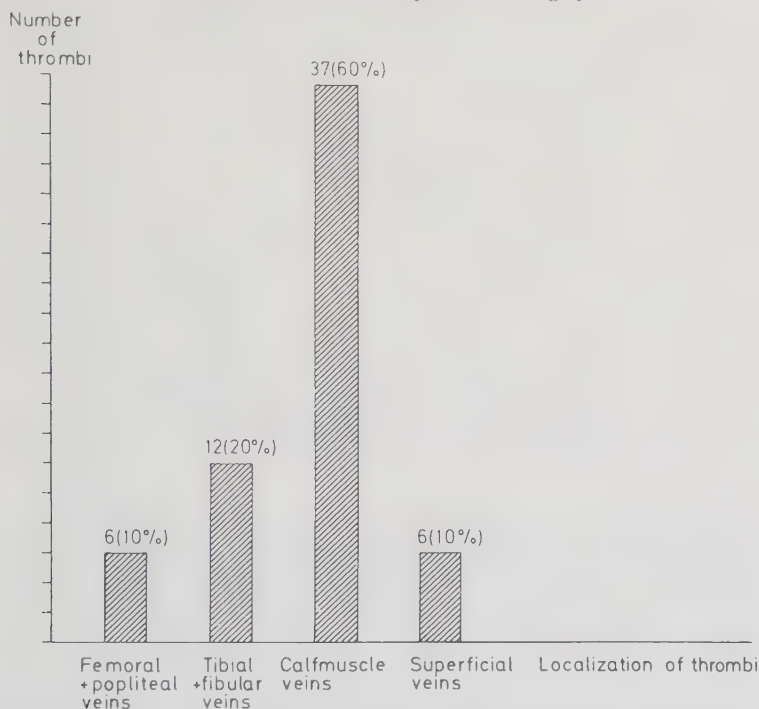


FIG. 1. Distribution of thrombi after gynecologic surgery initially diagnosed by ^{125}I -FUT. Four patients had only superficial venous thrombosis, whereas two had superficial thrombosis combined with DVT.

Age seemed to be an important factor in causing DVT. Patients more than 70 years old developed DVT in 31% of the cases, whereas for patients less than 70 years old the corresponding figure was only 12%. This difference is statistically significant ($P < 0.001$).

Neither weight, previous DVT, nor varicose veins had any significant influence on the frequency of postoperative DVT.

A most important finding was that patients treated preoperatively with estrogens developed postoperative thrombosis more often than those who had not, 39% versus 17%, respectively. The difference is statistically significant ($P < 0.01$).

There was no difference in the frequency of DVT between patients on prophylactic treatment with DHE and patients on prophylaxis with dextran, the figures being 23% and 20% respectively.

Twenty-two patients with phlebographically verified DVTs were treated with heparin.

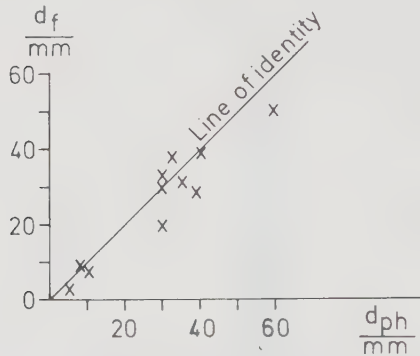


FIG. 2. Mean distances between 11 thrombi and skin surface of the medial side of the lower leg, as measured by phlebography and by the ^{125}I -fibrinogen sum coincidence method.

In 3 patients with positive leg scan signs of pulmonary embolism were diagnosed clinically and verified by lung scintigram. None of the patients was on anticoagulant therapy when the pulmonary embolism occurred. Two of the patients had received prophylaxis before the pulmonary embolism, one patient with Dextran and the other with DHE, but neither patient died.

Discussion

The results evidently show that the ^{125}I -FUTs, as we used them, are very sensitive and accurate in detecting and localizing DVT in the lower limbs after gynecologic surgery. Because of our positive experience with these methods, the techniques have now been introduced for routine use in our Department. This will certainly decrease the number of phlebographies needed to detect DVT after gynecologic surgery—a most satisfactory development in consideration of the disadvantages with this technique.^{6,7}

The overall incidence of thrombosis in this study, 17%, is not quite comparable with the results from other studies, since some patients in our study had received prophylaxis and others had not. However, the present results confirm the findings of Walsh et al.,⁸ who reported that patients with abdominal hysterectomies for malignant diseases have the highest postoperative frequency of DVT, whereas patients with only vaginal surgery for benign diseases have the lowest.

We could draw no definite conclusions concerning the effect of prophylactic treatment with DHE or dextran. If the advanced age and high proportion of malignant diseases in our patients are considered, our results agree with those

TABLE 2

Incidence of DVT Diagnosed by ¹²⁵I-FUT and Phlebography in 276 Patients After Gynecologic Surgery

	No. of Patients With DVT	Percentage DVT
Types of surgery		
Prolapses	28	15
Hysterectomies	19	22
Benign diseases	5	11
Malignant diseases	14	36
Without metastatic carcinoma	9	36
With metastatic carcinoma	5	36
Possible factors influencing DVT		
General anesthesia (prolapses)	14	14
Epidural anesthesia (prolapses)	14	16
Age > 70 years	22	31
Age < 70 years	25	12
> 100 minutes of operation	18	21
< 100 minutes of operation	29	15
Prophylaxis with dextran	9	20
Prophylaxis with DHE	9	23
Previous DVT	8	27
Varicose veins	35	21
Preoperative estrogens	12	39
No preoperative estrogens	35	14
Total	47	17%

Statistical comparisons were made with the χ^2 test with Yates's correction $P < 0.05$ was considered significant.

reported by McCarthy et al.⁹ and by Ruckley et al.¹⁰ In the study of McCarthy et al.⁹ the frequency of DVT in patients treated with dextran was 16.2% and in the study of Ruckley,¹⁰ 22%. In another study by Bonnar et al.,¹¹ the frequency of DVT in the group treated with Dextran was only 0.8%, but all of these patients had benign diseases.

The effectiveness of DHE as a sole prophylactic agent in patients subjected to gynecologic surgery has not yet been proved. In a study performed by Buterman et al.,¹² 7% of the patients developed postoperative DVT, but the mean age of these patients was only 45 years and the proportion of malignant diseases was not mentioned. We have, however, been able to verify the findings by Ballard et al.¹³ and McCarthy et al.⁹ that advanced age is an important risk factor, and we can also confirm the findings of the same authors that neither weight nor the type of anesthesia seems to influence the rate of postoperative DVT. Also in our study the duration of the operation did not seem to influence the development of thrombosis after surgery.

We find it very important that patients on preoperative estrogen therapy developed postoperative thrombosis much more often than those who were not. This points to the conclusion that any estrogen therapy should be completed before gynecologic surgery.

It is also important to point out that 33% of the thrombi were detected on the fifth to seventh postoperative day, that is, at a time when patients are often about to leave the hospital.

The ^{125}I -FUT, as we used it, is a very sensitive technique in detecting postoperative DVT, but it may be questioned whether the positive signs of thrombosis or fibrin deposits have any clinical value. It may then be argued that there was a close correlation between the ^{125}I -FUTs and phlebographies (Figure 2). Furthermore, because of the lack of sensitive methods suitable for repeated postoperative checkups, it is not possible to elucidate the course of even small untreated postoperative thrombi. In contrast to phlebography, our ^{125}I -FUT permits often repeated and proper follow-ups of the courses of even small DVTs. Before the results of such studies have been interpreted, it must be considered wise to treat even rather small DVTs with anticoagulants. The low frequency of pulmonary embolism in our study (about 1%), in spite of a rather high DVT rate, might then be ascribed to the positive effect of early treatment with heparin.

Kurt Bernstein, M.B.B.S., F.I.C.A.
University of Lund
Department of Obstetrics and Gynecology
S-214 01 Malmö, Sweden

References

1. Bernstein, K., Mattsson S., Ulmsten, U., et al.: The ^{125}I -fibrinogen method for early diagnosis of venous thrombosis. *Vasc. Surg.*, 13: 33, 1979.
2. Jacobsson, L., Mattsson, S., Bernstein, K., et al.: A method for determination of the depth of thrombi after injection of ^{125}I -fibrinogen. *Br. J. Radiol.* 53: 668, 1980.
3. McFarlane, A.S.: Labelling of plasma proteins with radioactive iodine. *Biochem. J.*, 62: 135, 1956.
4. Negus, D., Pinto, D.J., Le Quesne, L.P., et al.: ^{125}I -labelled fibrinogen in the diagnosis of deep vein thrombosis and its correlation with phlebography. *Br. J. Surg.*, 55: 835, 1968.
5. Nylander, G.: Phlebographic diagnosis of acute deep leg thrombosis. *Acta Chir. Scand. Supplement*, 387: 30, 1967.
6. Albrechtsson, U., Olsson, C.G.: Thrombotic side-effects of lower-limb phlebography. *Lancet*, 1: 723, 1976.
7. Olsson, C.G.: On the diagnosis of deep vein thrombosis. Dissertation, Department of Clinical Physiology, University of Lund, 1979.
8. Walsh, J.J., Bonnar, J., Wright, F.W.: A study of pulmonary embolism and deep vein thrombosis after major gynaecological surgery using labelled fibrinogen-phlebography and lung scanning. *J. Obstet. Gynaecol. Br. Cwlth.*, 81: 311, 1974.
9. McCarthy, T.G., McQueen, J., Johnstone, F.D., et al.: A comparison of low-dose subcutaneous heparin and intravenous dextran 70 in the prophylaxis of deep venous thrombosis after gynaecological surgery. *J. Obstet. Gynaecol. Br. Cwlth.*, 81: 486, 1974.
10. Ruckley, C.V.: Heparin v/s dextran in the prevention of deep vein thrombosis. A multi-unit controlled trial. *Lancet*, 2: 118, 1974.
11. Bonnar, J., Walsh, J.: Prevention of thrombosis after pelvic surgery by British Dextran 70. *Lancet*, 2: 614, 1972.
12. Butterman, J.A.G., Weldenbach, A., Gmelner, F.: Optimierung der postoperativen Thromboseprophylaxe in der Gynäkologie. Ein Vergleich von Heparin, Dihydroergotamin, ihrer Kombination und Azetylsalizylsäure. *Geburtsh. u. Frauenheilk.*, 38: 98, 1978.
13. Ballard, R.M., et al: Low doses of subcutaneous heparin in the prevention of deep vein thrombosis after gynaecological surgery. *J. Obstet. Gynaecol. Br. Cwlth.*, 80: 469, 1973.

ESTROGENS AND POSTOPERATIVE THROMBOSIS EVALUATED BY THE RADIOACTIVE IODINE METHOD

B. Åstedt, M.D., *Lund, Sweden*, K. Bernstein, M.D., B. Casslén, M.D., and
U. Ulmsten, M.D., *Malmö, Sweden*

THE ADMINISTRATION of estrogens has been related to an increase in the frequency of thrombosis in certain clinical conditions. The increased frequency of thrombosis in the puerperium period is still higher in women given diethylstilbestrol and ethinyl estradiol to suppress lactation. Oliver (13) found the frequency of thrombotic conditions increased in men treated with ethinyl estradiol to depress the blood cholesterol level. Bailar (3) found the use of diethylstilbestrol in the treatment of carcinoma of the prostate increase the mortality due to cardiovascular complications. Gow and MacGillivray (8) reported a high incidence of venous thrombotic disease in women after oophorectomy who were treated with ethinyl estradiol. Furthermore, the estrogenic component of oral contraceptives has been held responsible for its possibly thrombogenic effect. This effect is, however, refuted by Drill (5, 6) and Fuertes-de la Haba and associates (7).

Surgical procedures add an increased risk of thrombosis. In women requiring operations for prolapse of the uterus, there is also an indication for the administration of estrogens preoperatively to vitalize an atrophic vaginal mucosa. Such treatment might increase the risk of thrombosis.

In the present investigation, the aim was to investigate, by means of an improved ^{125}I -fibrinogen uptake test (4) and phlebography, whether or not fibrin deposits occurred more frequently after gynecologic surgical procedures in patients treated with estrogen than in those in a control group.

MATERIAL AND METHODS

There were 176 postmenopausal women in this investigation, 19 of whom were treated preoperatively with estrogen because of atrophic vaginal mucosa. All of them were more than 50 years of age and healthy, other than for prolapse of the uterus. All patients were operated upon ac-

cording to the standard Manchester technique. The patients were operated upon in the gynecologic position, using leg bearers. Full or epidural anesthesia was used. Body weight and the duration of the operation were recorded.

Estrogens were administered in two routine ways used at our clinic and, thus, not especially designed for the study. Eleven women received 50 micrograms of ethinyl estradiol daily for three weeks. Eight women received 200 micrograms of estradiol daily for 12 days. The remaining 157 women who received no hormonal treatment served as the controls.

Fibrin deposits were detected postoperatively. Fibrinogen was labeled according to the iodine monochloride method of McFarlane (11) and kindly provided by Doctor Thorell of the Department of Nuclear Medicine, Malmö, Sweden. The clotability of fibrinogen was found to be approximately 92 per cent. On the day before operation, the thyroid was blocked by an oral dose of 0.3 gram potassium iodine. The same amount was given daily for two weeks postoperatively. One hundred microcuries of ^{125}I -fibrinogen were injected intravenously on the evening before operation. Measurements were then performed on the following day immediately before operation and, again, on days 3, 5 and 7. The recordings were made by a technique previously described in detail (4).

Phlebography was performed according to the method of Nylander (12) using Isopaque Cerebral, metrizoate meglumine. Injection was done in a vein of the foot. Phlebography was performed upon all patients in whom fibrin deposits were detected by the ^{125}I method. For statistical calculation, the χ^2 -test with Yates' correction was used.

RESULTS

In the group of women treated with 50 micrograms of ethinyl estradiol daily for three weeks, fibrin deposits were found in six of the 11 patients. Of those receiving 200 micrograms of ethinyl estradiol daily for 12 days, fibrin deposits

From the Departments of Gynecology and Obstetrics, University of Lund, Allmänna Sjukhuset, Malmö, and Lasaretten, Lund.

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were found in four of eight. Corresponding figures for the control group were 18 of 157. The increased frequency of fibrin deposits between the estrogen groups compared with that for the control group was significant, $p < 0.001$. Due to this observation, the study was discontinued.

In all patients, the fibrin deposits could be verified by phlebography. In five of the patients treated with estrogen, the fibrin deposits were localized in the tibial veins and in five, in veins of the calf muscle.

The duration of the operation and the distribution of body weight and the duration of general and epidural anesthesia were similar in the treated and the control groups. Patients in whom fibrin deposits were detected were treated with heparin, and fatal complications occurred in none.

DISCUSSION

The results show that the frequency of detectable fibrin deposits after gynecologic operations was higher in both estrogen treated groups compared with the control group. Possible thrombosis disposing factors, such as body weight, duration of operation and methods of anesthesia, were equally distributed among the groups. It is of interest that not only the dose but also the duration of preoperative estrogen treatment seems to be important.

The ^{125}I -fibrinogen uptake test used in the present study is quite sensitive and can, with modifications, even be used for deep localization of thrombi (4, 10). It may be argued that some of the thrombi revealed by this technique were so small that they were of no, or minor, clinical importance. However, all could be visualized by phlebography. Aside from phlebography, no reliable method for the objective determination and observation of the course of a thrombosis exists. Since the improved ^{125}I -fibrinogen uptake test technique enables recordings for a long time with high sensitivity, it is possible to observe the course of the detected thrombosis. Thus, the method offers a new possibility to study initiation, development and results of treatment of thrombosis. Before such studies had been carried out, it was almost impossible to predict the clinical importance and course of small thromboses or fibrin deposits.

The question arises regarding, in which way, estrogens further increase the postoperative frequency of fibrin deposits. Thrombogenesis is known to be multifactorial. It has, however, been shown that an intact fibrinolytic defense system is important in the prevention of thromboses of vari-

ous origins. This defense system is initiated by fibrinolytic activators contained in the vessel walls. Early fibrin deposits which might occur on the endothelium of the vessel wall, thus, be continuously dissolved and removed if sufficient amounts of activators are present. The majority of patients with recurrent thromboses has been found by Isacson and Nilsson (9) to have a low content of fibrinolytic activators in the vessel walls.

It has also been shown that ethinyl estradiol administered in a large dosage is able to depress the fibrinolytic activator content in the vessel wall (2). Furthermore, a decrease in fibrinolytic activators in the vessel has been found by Åberg and colleagues (1) at operation. Thus, operation and the administration of ethinyl estradiol may have synergistically depressed the fibrinolytic defense system against thrombosis. In the postoperative period and after discontinuation of ethinyl estradiol, the fibrinolytic activator content returns to normal. It is, therefore, an open question as to whether or not all, or any, of the instances of thrombosis detected by the ^{125}I -method would have been manifested clinically. Estrogens should not, in any event, be given preoperatively, and if administered as an oral contraceptive or for climacteric inconvenience, they should be discontinued preoperatively.

SUMMARY

Women who were to be operated upon for prolapse of the uterus were treated preoperatively with estrogens for atrophic vaginal mucosa and examined postoperatively by the ^{125}I -fibrinogen uptake test and phlebography. Among 11 women who received 50 micrograms of ethinyl estradiol daily for three weeks, fibrin deposits were found in six. Of eight women receiving 200 micrograms daily for 12 days, such deposits developed in four. Corresponding figures for the control group were 18 of 157, $p < 0.001$. Estrogens, therefore, should not be given preoperatively, and those patients treated with preparations containing estrogens should have such therapy discontinued preoperatively.

REFERENCES

1. ÅBERG, M., ISACSON, S., and NILSSON, I. M. The fibrinolytic system and postoperative thrombosis following operation of rectal carcinoma. *Acta Chir. Scand.*, 1974, 140: 352.
2. ÅSTEDT, B. Low fibrinolytic activity of veins during treatment with ethinyl-oestradiol. *Acta Obstet. Gynecol. Scand.*, 1971, 50: 279.
3. BAILLAR, J. C. Thromboembolism and oestrogen therapy. *Lancet*, 1967, 2: 560.

4. BERNSTEIN, K., MATTSSON, S., ULMSTEN, U., and ÅSTEDT, B. The ^{125}I -fibrinogen method for early diagnosis of venous thrombosis. *Vasc. Surg.*, 1979, 13: 33.
5. DRILL, V. A. Oral contraceptives and thromboembolic disease—I, prospective and retrospective studies. *J. A. M. A.*, 1972, 219: 583.
6. DRILL, V. A., and CALHOUN, D. W. Oral contraceptives and thromboembolic disease—II, estrogen content of oral contraceptives. *J. A. M. A.*, 1972, 219: 593.
7. FUERTES-DE LA HABA, A., CURET, J. O., PELEGRINA, I., and BANDIWALA, I. Thrombophlebitis among oral and nonoral contraceptive users. *Obstet. Gynecol.*, 1973, 38: 259.
8. GOW, S., and MacGILLIVRAY, I. Metabolic, hormonal, and vascular changes after synthetic oestrogen therapy in oophorectomized women. *Br. Med. J.*, 1971, 2: 73.
9. ISACSON, S., and NILSSON, I. M. Defective fibrinolysis in blood and vein walls in recurrent "idiopathic" venous thrombosis. *Acta Chir. Scand.*, 1972, 138: 313.
10. JACOBSSON, L., MATTSSON, S., BERNSTEIN, K., and others. Method for determination of depth of thrombi after injection of ^{125}I -fibrinogen. *Br. J. Radiol.*, in press.
11. McFARLANE, A. S. Labelling of plasma proteins with radioactive iodine. *Biochem. J.*, 1956, 62: 135.
12. NYLANDER, G. Phlebographic diagnosis of acute deep leg thrombosis. *Acta Chir. Scand.*, 1968, Suppl. 387: 30.
13. OLIVER, M. F. Thrombosis and oestrogens. *Lancet*, 1967, 2: 510.



DEPTH LOCALIZATION OF THROMBI AND DYNAMIC STUDIES OF POSTOPERATIVE
THROMBOSIS USING THE ^{125}I -FIBRINOGEN-SUM-COINCIDENCE METHOD

K. Bernstein, L. Jacobsson., S. Mattsson and U. Ulmsten

Departments of Anaesthesia, Obstetrics and Gynaecology and
Radiation Physics

Malmö General Hospital

S-214 01 MALMÖ

Sweden

INTRODUCTION

Recently we have introduced a new technique, the ^{125}I -fibrinogen-sum-coincidence method (FSC), which can be used in combination with the conventional fibrinogen uptake test (FUT) for detecting deep venous thrombosis (DVT) ¹. With this new method, it is possible to determine the depths of the fibrin deposits detected by FUT. This is most important since it permits differentiation between true DVT and superficial venous thrombosis. In addition, the new method also reduces the number of false positive fibrinogen uptake tests caused by inflammatory skin lesions, inflammatory joint diseases and varicose veins. Very good agreement has been demonstrated between depth determinations of thrombi by the FSC-technique and by phlebography ^{1,2}.

Also important is the fact that the new method offers the possibilities of both determining the true ^{125}I activity in a thrombus and following its course for several weeks.

As a continuation of our earlier studies with the FSC technique, the following aims were set up:

1. To analyse the possible benefits of detection of DVT by the FSC technique in combination with conventional FUT.
2. To study the long-time course of postoperative thrombi.

MATERIAL AND METHODS

354 patients admitted consecutively for gynaecologic surgery were screened for postoperative DVT with an improved FUT ³ to detect thrombosis. 65 patients were found to have positive signs of lower limb DVT, 41 patients were checked by the FSC technique as well. 22 consecutive patients (24 thrombi) were studied with FSC and phlebographies in order to determine the depths of the thrombi.

The patients were investigated as follows:

The legs were screened using the improved conventional ^{125}I -FUT described previously ³. After oral blocking of the thyroid with 0.3 g potassium-iodide, (the same amount of potassium-iodide was then given daily for 14 days), 4 MBq ^{125}I -fibrinogen were injected intravenously on the evening of the day before surgery. Recordings were made immediately before surgery and then postoperatively on days 1, 3, 5 and 7. An increase on two consecutive days in the percentage count rate of 10 per cent units or more compared to the preoperative value was

suggestive of thrombosis³. When positive signs of DVT were found in conventional ¹²⁵I-FUT, the areas with the highest count rates were localized and examined with the FSC technique.

The basic principles of the ¹²⁵I-fibrinogen-sum-coincidence technique (FSC) have been described elsewhere¹. By taking the ratio between the number of coincident photons registered (N_c) and the total number of photons recorded (N_t), a parameter is obtained which is very sensitive to the distance between the detector and the source of emission. The measurements were carried out in a low background room. The detector used was an Na(Tl) crystal with 124 mm diameter and 1.5 mm thickness, equipped with a brass collimator 50 mm long and 5 mm thick and with a central opening of diameter 40 mm.

Clinically, the FSC technique was applied as follows:
The count rate of the corresponding area of the contralateral leg free of thrombus was used as a background. When this count rate was subtracted from the count rate over the thrombus, it was possible from the excess counts recorded to determine N_c/N_t and hence to calculate the depth and net-activity of the thrombus¹. The mean values and standard deviations of the depth of thrombi from both the medial and posterior sides of the skin surface of the lower limb were calculated. The values obtained were checked by phlebography. For comparison mean values and standard deviations of the effective depths of the "background" activity from blood and normal tissue of 33 lower limbs without any signs of thrombosis were also calculated. These recordings were made over three predetermined areas in the calf³, from the medial side in 33 legs (71 recordings) and from the posterior side in 17 legs (17 recordings). Over three areas³ in 15 thighs, altogether 45 recordings were made.

Phlebography was performed according to the technique described by Nylander⁴ and when the thrombus was clearly visible, depth measurement was made directly on the X-ray picture with proper correction for the scale factor.

The dynamic studies were performed on 17 patients with altogether 19 thrombi. These patients were followed up once a week with the FSC method. Seven thrombi were followed for 2 weeks after surgery and 12 for 4 weeks. Of the 17 patients with DVT, 11 patients received prophylactic treatment with sodiumheparin: Five received heparin 5 000 IU x 2 S.C., 3 heparin 5 000 IU x 3 S.C. and 3 heparin 12 000 IU x 2 S.C. The remaining 6 patients were not treated. No screening for PE was done,

but clinical signs of PE were looked for during the first month after operation. The diagnosis of PE was confirmed by lungscintigraphy.

The maximum net activity of a thrombus ($A_{\max}$) was calculated as was the effective half life of its ^{125}I -fibrinogen content (T_t) in the period 7 - 21 days after operation. The effective half lives of the corresponding background radiations of legs free of thrombus (T_b) were also determined. Linear regression analysis and Student's T-test were used for statistical calculations.

RESULTS

24 DVT:s in the calf were located at an average depth of 38.6 ± 7.9 mm (S.D) from the medial side of the skin surface. When the depths of 18 of these thrombi were determined from the posterior side of skin surface they were found to be located 40.7 ± 9.7 mm from that surface. All thrombi were verified phlebographically and a close correlation was found between the depths measured by the two methods in 14 patients with 16 thrombi. (Table 1). The depths of the rest of the thrombi could not be measured on their respective phlebograms. As seen in table I three legs with clinically evident superficial venous thrombosis had their fibrin deposits located very superficial: 1, 7 and 9 mm respectively from the skin surface. The radiation from a true DVT was localized much deeper in the lower limb than that emanating from normal tissues, the difference being statistically significant ($p < 0.001$). (Table II). (This difference was utilized as an additional criterion for the presence of DVT).

There was no change in the depths of the ^{125}I activity of normal tissue between pre- and postoperative measurements. (Table II).

In the long term study, three types of thrombi called A, B and C could be differentiated. Each type represented thrombi of different degrees of severity. As seen in figure 1, already on the first postoperative day, the patient with thrombus A had an increased ^{125}I -fibrinogen uptake indicating a thrombosis in the popliteal region. Phlebography also demonstrated a thrombus in the deep calf veins extending into the popliteal vein. This patient was immediately treated with low dose heparin (5 000 IU x 2 S.C.). A slow decrease in activity occurred ($T_{1/2} = 12$ days). On the 18th day after surgery, pulmonary embolism

occurred and the patient then received full dose heparin. After this treatment was started, an increased elimination rate of ^{125}I was recorded ($T_{1/2} = 6.4$ days), and the further clinical course was uneventful.

Table I. Phlebographic localization of 16 thrombi in 14 patients. The depths from the skin surface of the calf have been measured on the phlebograms as well as by the ^{125}I -fibrinogen-sum-coincidence method.

Pat. nr.	Phlebographic localization of the thrombus	Phlebography	^{125}I -fibrinogen- sum-coincidence method
		<u>Depth</u> mm	<u>Depth</u> mm
1	calf muscle vein	25	24 ± 1
2	calf muscle vein	30	30 ± 1
3	calf muscle vein	35	31 ± 3
4	calf muscle vein	58	50 + 20 - 10
5	a) calf muscle vein	*	} 30 + 6 - 3
	b) fibular vein	60	
6	fibular vein	40	38 + 7 - 4
7	a) post. tibial vein	30-35	38 + 7 - 4
	b) superficial thrombophlebitis	5 - 15	7
8	calf muscle vein	20 - 40	31 + 4 - 3
9	calf muscle vein	35 - 42	29 ± 3
10	post. tibial vein	30	33 + 12 - 7
11	superficial thrombophlebitis	superficial	1
12	large saphenous vein	superficial	9
13	calf muscle vein	55	43 + 13 - 7
14	calf muscle vein	30 - 35	31 + 5 - 7

* No exact measurement could be done

Table II. Mean depths of thrombi in the lower limbs as measured from both the medial and posterior side of the leg by the ^{125}I -fibrinogen-sum coincidence method are compared with the mean depth of ^{125}I -activities in the tissues of corresponding areas of legs free of thrombus. Student's T-test was used in the statistical calculations.

Site of recording	Mean depth of thrombi mm	Mean depth of ^{125}I - activity in legs free of thrombus mm	
Medial side of the calf (areas 2,3,4) ³	38.6 $\pm$ 7.9 N = 24	21.3 $\pm$ 3.1 n = 71	P<0.001
Posterior side of the calf (areas 2,3,4) ³	40.7 $\pm$ 9.7 n = 18	21.2 $\pm$ 3.5 n = 17	P<0.001
Medial side of the thigh (areas 6,7,8) ³	-	26.3 $\pm$ 4.3 n = 45	
<u>Preop.:</u>			
Medial side of the calf (areas 2,3,4) ³	-	22.2 $\pm$ 2.0 n = 30	N.S.
<u>Postop.:</u> (8th day)			
Medial side of the calf (areas 2,3,4) ³		19.1 $\pm$ 5.0 n = 30	

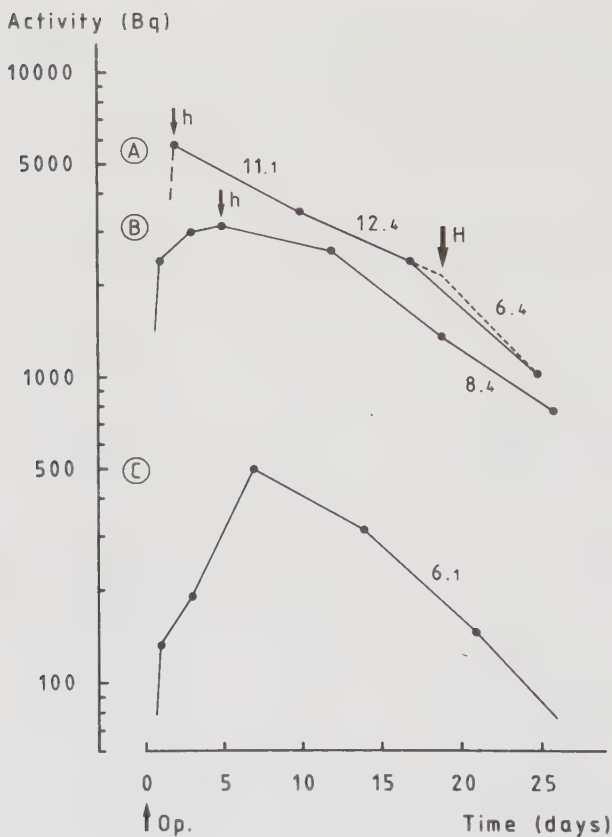


Figure 1.

Net ^{125}I activity of thrombi in 3 patients (A,B and C) at various times after injection of ^{125}I -fibrinogen.

The time of surgery (op.) is indicated in the figure as well as the estimated "effective half life" in days of ^{125}I at various time intervals,

The "effective half life" of ^{125}I in the blood of patient A was 3.2 days, of patient B 4.6 days and of patient C 4.0 days.

H. indicates the start of full dose heparin treatment;

h start of low dose heparin treatment.

The patient with thrombus B in figure 1 had an increased ^{125}I -uptake in the calf on the third postoperative day. Phlebography verified the presence of a thrombus in the posterior tibial vein. Low dose heparin was given from day 5. Between day 12 and 30, an effective half life of 8.4 days was observed. The clinical course was uneventful.

Fifteen thrombi (types A and B) contained maximal ^{125}I activities of between 2 and 8 kBq. These were classified as major ones and were all located in the deep calf veins. Three of them induced manifest pulmonary embolism.

Four small thrombi (type C) were found. These thrombi contained a maximum activity of about 800 Bq (2/10 000 of injected activity) and lysed spontaneously within 2 - 4 weeks (Fig 1). Maximum net activities of thrombi were also plotted against their T_t/T_b ratios in a log-log diagram (fig. 2). As can be seen from figure 2, a linear relationship exists between the maximum net activities of the thrombi and their corresponding half life ratios. The equation is shown on figure 2. The correlation coefficient was found to be 0.80 and the correlation highly significant ($p < 0.001$).

DISCUSSION

From figure 2, it is evident that the half life of small thrombi (T_t) is the same as for blood (T_b). Let us assume that larger thrombi are composed of a surface layer with a complete exchange of ^{125}I -fibrinogen between it and the blood and a central core with ^{125}I -fibrinogen not available for exchange with the blood. The "effective" exchange rate ($\lambda_t = \frac{\ln 2}{T_t}$) of ^{125}I from the whole thrombus may then be written as:

$$\lambda_t = \frac{\lambda_b \cdot 4\pi r^2 \cdot \Delta r}{\frac{4}{3}\pi r^3} \quad (1)$$

where λ_b is the elimination rate of ^{125}I -fibrinogen in blood, r the radius of the thrombus and Δr the thickness of the surface layer.

From equation 1, it is evident that T_t/T_b is proportional to r for constant Δr . The maximum activity, $A_{\max}$, is assumed to be proportional to r^3 and hence our simple theory explains why $A_{\max}$ should be proportional to $(T_t/T_b)^3$. This is also found in figure 2.

Maximal ^{125}I activity in thrombus (A_{max})
k Bq

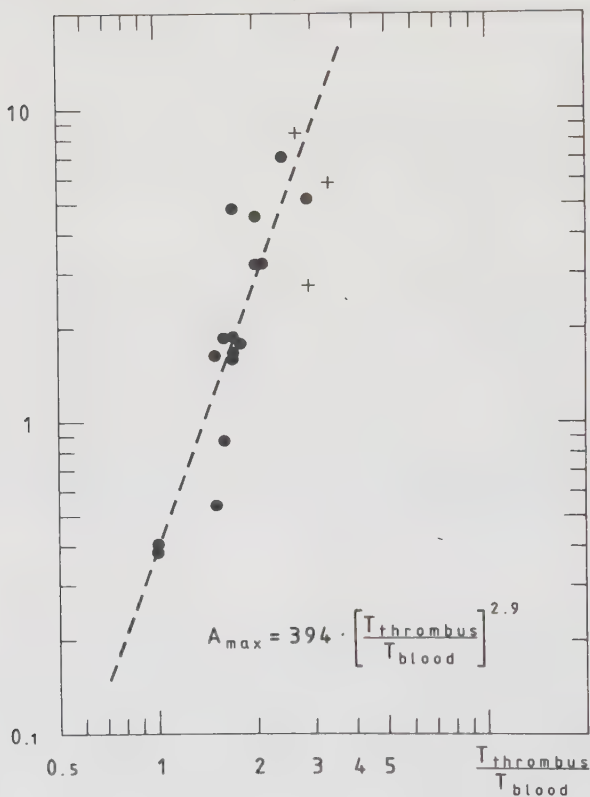


Figure 2. Relation between ^{125}I activity of a thrombus and its "effective half life" T_t divided by the "effective half life" of ^{125}I in normal tissue T_b . Crosses indicate thrombi inducing pulmonary emboli. Linear regression analysis was used in statistical calculations. The three thrombi which led to pulmonary embolism were excluded from the statistical calculations.

From both the present and the previous results¹, it is evident that with the FSC technique it is possible to differentiate between deep venous thrombosis and superficial venous thrombosis in a simple manner. However, since the thrombi are well separated in depth from the background radiation of the corresponding areas in legs free of thrombus, we wish to emphasise that further diagnostic information is made available by the present technique. To our previous criteria suggestive of thrombosis³, we can now add the following:

If the excess activity detected by the conventional fibrinogen uptake test is located deeper than 28 mm ($21.3 + 2$ S.D) from either the medial or the posterior side of the skin surface of the lower limb, this is suggestive of DVT. If, on the other hand, the excess activity is located less than 14 mm ($21.3 - 2$ S.D) from the skin surface on either the medial or posterior sides of the lower limb, this is suggestive of superficial inflammatory reaction. Furthermore, the new technique increases the reliability of the conventional ¹²⁵I-fibrinogen uptake test by reducing the number of false positive results due to superficial venous thrombosis, inflammatory skin lesions, varicose veins, and generally enhanced ¹²⁵I-fibrinogen uptake in a leg due to e.g. edema.

So far, comparatively little information has been gained about the course of postoperative DVT detected by conventional ¹²⁵I-FUT. About one-third of the DVT:s detected by this method has been considered to lyse spontaneously during the first postoperative week^{5,6}, but the further course of postoperative DVT has not been assessed by this method. Phlebographic studies of DVT have been carried out⁷, but since this technique is not suited for postoperative screening, only limited information has been obtained.

The present study proves that with the FSC technique it is possible to follow postoperative thrombi for up to one month after surgery. It is of fundamental importance that this technique gives the possibility of measuring the true ¹²⁵I activity of a thrombus. This is not possible with the conventional technique for FUT studies. The true maximum net activity of a thrombus might give an indication of its severity, since the three thrombi who induced pulmonary emboli had high net activities. On the other hand, thrombi with small net activities were all fibrinolysed spontaneously within one month. By screening

for PE in a greater number of patients with DVT it might be possible to draw more safe conclusions about the predictive value of the FSC-test.

Used in conjunction with the ^{125}I -fibrinogen-sum-coincidence method (FSC), the ^{125}I -fibrinogen method is comparable to phlebography in accuracy but has many advantages compared with this latter; it is a non invasive technique, it is easy to perform and it does not require a skilled interpreter as phlebographies do. Last but not least, it is not painful to the patient and can easily be repeated when desired. A mobile unit, which makes all the necessary measurements and computes the results, is at present being constructed.*

With this equipment measurements can be done outside a background shielded room.

* For sale by Therados Instrument AB, Dalgatan 15,
S-752 28 UPPSALA, Sweden

REFERENCES

1. Jacobsson, L., Mattsson, S., Bernstein, K., Ulmsten, U., and Åstedt, B.: A method for determination of the depth of thrombi after injection of fibrinogen labelled with iodine-125. BRIT. J. RADIOL. 53:668, 1980
2. Bernstein, K., Ulmsten, U., Åstedt, B., Jacobsson, L., and Mattsson, S.: Incidence of thrombosis after gynecologic surgery evaluated by an improved ^{125}I -fibrinogen uptake test. ANGIOLOGY 31(9):606, 1980.
3. Bernstein, K., Mattsson, S., Ulmsten, U., and Åstedt, B.: The ^{125}I -fibrinogen method for early diagnosis of venous thrombosis. VASCULAR SURGERY 13(1):33, 1979
4. Nylander, G.: Phlebographic diagnosis of acute deep leg thrombosis. ACTA CHIR. SCAND. suppl 387:30, 1967
5. Kakkar, V.V., Howe, C.T., Flanc, C., and Clarke, M.B.: Natural history of postoperative deep-vein thrombosis. LANCET 2:230, 1969
6. Becker, J.: Postoperative venous thrombosis. ACTA CHIR. SCAND. suppl. 431:7, 1972
7. Becker, J., Borgström, S., and Saltzman, G.F.: Occurrence and course of thrombosis following prostatectomy. ACTA RADIOL. 10:513, 1970.

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3. The third part of the report deals with the financial statement of the year, and the results of the various projects.

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